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Cardiovascular Safety in Drug Development and Therapeutic Use

New Methodologies and Evolving Regulatory Landscapes

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ISBN 978-3-319-40345-8 ISBN 978-3-319-40347-2 (eBook)
DOI 10.1007/978-3-319-40347-2

Library of Congress Control Number: 2016944617

Printed on acid-free paper
Adis is a brand of Springer

This Adis imprint is published by Springer Nature
The registered company is Springer International Publishing AG Switzerland

Foreword

Throughout four billion years of trial and error, nature has done a pretty credible job of creating, from just half a dozen elemental building blocks, a set of several hundred drug receptors (many in families sharing many structural features) and a far smaller set of post-receptor effector systems. To obtain localization of action, nature invented layers of structure, from organelle to cell to organ. It should be no surprise, therefore, that drugs, i.e., exogenous compounds that interact with receptors, exist and that they are nonspecific. This arises from incomplete specificity for a receptor subtype, nonlocalized delivery, and common selectivity features shared by otherwise unrelated receptors. Such lack of specificity of action is predictably worse for small-molecule drugs, whose receptor affinity depends upon fewer of the receptor's selectivity features (see Chap. 2 for a fuller discussion). Clever medicinal chemists employ a variety of techniques involving some insight into the receptor structure and brute-force testing of thousands of compounds, but highly specific actions of drugs are rare.

Off-target effects give rise to nuisance effects at best and, at worst, to catastrophic adverse clinical effects that are more consequential than hoped-for benefits. Societal aspirations for "safe" drugs cannot be satisfied: what one can do is identify drugs whose benefits in a population (not an individual) are apt to exceed their harms. Some off-target effects manifest in the cardiovascular system, an organ system with high metabolic turnover (a vulnerability), a rich set of feedback mechanisms (lots of receptors, providing opportunities for directly toxic effects), and load dependence on other things going on in the body (opportunity for indirect effects). Many are the opportunities for mayhem in the cardiovascular system.

How good are we at identifying cardiovascular risks of new drugs? There exists a quite robust framework around the determination of the benefits of a drug, as discussed in Chap. 4. Prospective design, randomization, blinding of subjects and investigators to treatment and to intermediate results, and replication of findings are common features of drug development programs: their primary goal is the

establishment of evidence that a particular benefit is attributable to the drug. We make less rigorous decisions about what dosing regimens to approve, how best to describe a drug's benefits, and to whom those benefits are likely to apply, but the framework allows one to describe how certain one is that the specific benefit is likely to be reproducible in practice. However, as noted in Chap. 5's discussions, safety is evaluated quite differently despite a much longer regulatory history for safety than for effectiveness. Instead of a hypothesis-testing paradigm as used for establishing benefit, there is a heuristic for safety evaluation that involves a variety of generally nonspecific assessments conducted in all phases of development, from nonclinical through Phase III trials and beyond. In general, we treat adverse observations as concerning, but the paradigm creates huge multiplicity problems (Chap. 4 introduced this issue) because the more times we ask a safety-related question, the more likely it becomes that one of the answers will indicate a spurious result, i.e., a finding that is not reproducible.

There are some exceptions to this general observation. Some targeted safety issues are addressed in a more rigorous manner. Two of them, described in great detail in this book, are interesting for multiple reasons. First, numerous drugs were removed from the market for causing a fatal arrhythmia, called torsades de pointe. This led to international guidance calling for careful assessment not of the arrhythmia itself (which is rare) but of a biomarker, the QT interval of the ECG. A threshold was set in the guidance that said if the drug effect on QT was smaller than about a 3% increase over baseline, the proarrhythmic risk was generally ignorable. A whole industry sprang up around doing studies capable of resolving such tiny effects, diverting resources from what are, arguably, bigger public health concerns (see, e.g., discussions in Chaps. 11 and 14), but, worse, getting the answer wrong sometimes. That is, large effects on QT are almost certainly bad, but small effects can be benign. Because there now exists a very deep understanding of what makes one drug proarrhythmic and another not, it is clearly possible to design nonclinical assessments that reliably distinguish the level of risk, and engineering work in this area is ongoing, as described in discussions in Chap. 9 of the Comprehensive in vitro Proarrhythmia Assay (CiPA).

The second example of a safety issue being addressed with some degree of statistical rigor is the risk of death, myocardial infarction, and stroke associated with anti-glycemic drugs used to treat diabetes. Guidance in the USA calls for ruling out some degree of excess risk preapproval and then ruling out a lower risk postapproval. This requirement remains in effect at the time of writing despite the fact that studies to date have either shown no harm or have shown benefit and despite the fact that the original finding that stimulated concern has been refuted: Chaps. 12 and 13 cover this topic.

There is ongoing debate regarding when to demand cardiovascular safety outcome studies. Some individuals have taken the position that they should be the rule rather than the exception. However, this would vastly increase the cost of drug development, and, based on the frequency with which important safety

signals are discovered late, such measures would have little return. On the whole, the usual paradigm, while based on a gestalt interpretation of many different assessments, serves society pretty well. Furthermore, CiPA is probably not the only aspect of cardiovascular safety that is amenable to mechanistically targeted assessments of drug effects on human effector systems in vitro, rather than through whole animal studies. Look for additional examples in future editions of this book!

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Dr Stockbridge is director of the Division of Cardiovascular and Renal Products, Center for Drug Evaluation and Research, Food and Drug Administration. Opinions expressed here are those of the author and do not represent those of the FDA.

Preface

This book is a self-contained introduction to, and exposition of, the field of biopharmaceutical cardiovascular safety. While drugs for cardiovascular diseases or conditions of clinical concern are expected to affect the cardiovascular system, drugs for other indications are not. However, there is always the possibility that a noncardiovascular drug can exert a deleterious influence on one or more parts of the cardiovascular system, and, while rare, some drug-induced cardiac adverse events can be fatal. The field of cardiovascular safety, of which proarrhythmic cardiac safety is an important component, has therefore assumed considerable importance in contemporary drug development and therapeutic use. Not everyone needs to be an expert in cardiovascular safety (and this book by itself does not presume to make anyone an expert), but everyone can benefit from a fundamental knowledge of the field.

Different aspects of the book's conceptual and organizational architecture reflect our endeavors to optimize its benefit to different readerships. Following the initial chapter that provides context for all subsequent discussions, the next five chapters review biological considerations (Part II of the book) and statistical considerations (Part III) underlying the investigations reported in Parts IV, V, and VI. These chapters are tailored for students of medicine, pharmacy, nursing, and all allied health professions and for seasoned professionals who may wish to refresh or extend their knowledge of these topics. Many readers may be familiar with some of this material already and can progress towards Parts IV, V, and VI, accordingly. These chapters can also be useful "reference guides" when encountering discussions involving material they cover in later chapters.

As is typical for scholarly works, references are provided for materials discussed in the main text of each chapter: in total, there are approximately 500 of these. Additionally, for readers already involved in the field of cardiovascular safety, and for students who wish to become particularly familiar with one or more topics in greater detail, extensive further reading lists are provided at the end of chapters: these materials relate to discussions in respective chapters, but are not cited within the chapters. In total, approximately 900 further readings are provided. These lists have several purposes: to enable inclusion of the work of as many colleagues as possible, to demonstrate the wide range of journals in which their work is published,

and to make the book's content as up to date as possible. The last task we completed before submitting the manuscript to our publisher was to use the PubMed search engine to find papers that had been e-published very shortly before submission. While those that had subsequently been published in print were updated to provide the full citation information when reading the book's galley proofs, the others can still be located on PubMed via the information provided.

It is an exciting time in the domain of cardiac safety. Since the release in 2005 of the ICH Guideline E14 and its subsequent adoption by regulatory agencies, the primary methodology for the prospective exoneration of a new drug from an unacceptable cardiac safety liability has been the Thorough QT/QTc Study, a randomized, active- and placebo-controlled clinical trial. Chapter 7 discusses the genesis of ICH E14 and an associated guideline, ICH S7B, which addresses nonclinical cardiac safety investigations. However, a major step in the evolution of clinical proarrhythmic cardiac safety methodologies occurred during the preparation of this book in December 2015, leading the first drafts of several chapters to be updated accordingly. That month saw the release of the third revision to a "Question & Answers" document associated with ICH E14. A second methodology, exposure–response modeling, was introduced, and, as we write this Preface, regulatory agencies have already found studies utilizing this methodology to be acceptable for this purpose. This methodology is discussed in Chap. 8. Also, many colleagues are currently working hard in the development and evaluation of a new methodology in the nonclinical proarrhythmic cardiac safety domain: the Comprehensive in vitro Proarrhythmia Assay (CiPA) paradigm is described in Chap. 9.

Chapter 10 discusses the field of cardio-oncology. Many oncologic drugs are well known to be cardiotoxic, but, since they offer live-saving therapeutic benefits, the overall benefit–risk balance of their administration is often considered favorable. However, attention must be paid to patients' cardiovascular health, both during therapy and after treatment cessation, since cardiovascular complications can emerge shortly after treatment onset in some individuals and much later in other individuals who have been cancer-free for many years. Close collaboration between oncologists and cardiologists is the hallmark of cardio-oncology.

Chapter 11 focuses on off-target, drug-induced increases in blood pressure. It has become clear that a wide range of drugs can lead to such changes. While they may be large in some individuals, and therefore readily detected in clinical practice, they may be relatively modest in other individuals. This makes their identification in clinical practice more problematic, even though, if identified, they may well be of clinical concern. If the drug leading to an identified increase in blood pressure is required for a patient's benefit, coadministration of antihypertensive therapy may be a suitable approach. This is an area where more research is needed.

Chapters 12 and 13 address the current regulatory landscapes that were put in place in the USA and Europe to provide a methodology for the prospective exoneration of a new antidiabetic drug for type 2 diabetes from an unacceptable cardiovascular safety liability. Chapter 12 details the genesis of these landscapes, while Chapter 13 discusses methods to satisfy their requirements most efficiently.

The final part of the book, comprising Chaps. 14 and 15, focuses on additional considerations in cardiovascular safety and other aspects of general drug safety during therapeutic use. As one example, the use of QT-prolonging drugs in hospital settings is of interest. First, how well do prescribing physicians comply with regulatory warnings in these drugs' labeling? Second, how well do physicians (cardiologists and noncardiologists) identify cases of QT prolongation from their inspections of electrocardiographic (ECG) recordings? The answers are less than comforting. As a second example, consider published reports of clinical trials. If a drug has any kind of safety liability that is identified in a clinical trial, one would hope that this is well documented ("the truth, the whole truth, and nothing but the truth") in the published journal paper reporting the study. Chapter 15 sheds light on this issue, and the light reveals rather disconcerting occurrences. We can do better.

As noted earlier in this Preface, not everyone needs to be an expert in cardiovascular safety. However, we hope that the following discussions will make readers at all levels of involvement with drug development and therapeutic use cognizant of the breadth and depth of the field and that it may encourage some readers to enter and/or pursue to a greater extent their involvement in the field. Biopharmaceutical medicine offers great therapeutic benefit to many millions of patients worldwide, but it is also a public health moral imperative that we do everything we possibly can to protect patients from avoidable adverse drug reactions.

Thank you very much for your interest in this book: we hope you find it useful in your scholarly and professional pursuits. The authors' remuneration has been donated to the American Heart Association.

Chapel Hill, NC, USA — J. Rick Turner
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March 2016

About the Authors

J. Rick Turner, BSc (Hons), PGCE, PhD, DSc, is an experimental research scientist, clinical trialist, author, editor, and educator. He spent the first part of his professional career in the field of cardiovascular behavioral medicine, detailing the individual differences apparent in cardiovascular responses to behavioral and psychological stressors, including genetic influences upon them. He received two international awards for his research and is coeditor of the 2013 Springer volume *Encyclopedia of Behavioral Medicine*, the definitive work in this area.

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Acknowledgments

This book was written at the suggestion of Carolyn Honour, Managing Director, Springer Healthcare. The fields of cardiac and cardiovascular safety have evolved considerably in recent years, and an up-to-date review is therefore timely. We thank Carolyn for her invitation, Cameron Wright for shepherding the book manuscript through the publication process, and everyone else at Springer, Adis and Spi Global for their contributions.

Several colleagues made important contributions to chapters and are regarded as coauthors of the respective chapters. These include Niketa Godse and Ganesh Gundi (Chap. 7), Gary Gintant (Chap. 9), Ron Lieberman and Gopi Krishna Panicker (Chap. 10), Eoin O'Brien (Chap. 11), and Mary Jane Geiger and Cyrus Mehta (Chap. 13). Allen Kindman, John Lee, and Jared Schettler reviewed other sections of the text. Jim Chestnut and Benjy Stein at Quintiles' library services provided outstanding literature review services. Michael Weber provided Expert Opinion for Chap. 11.

The nature of the book, which is one of inclusiveness, collaboration, and integration, means that we owe a debt of gratitude to all of the researchers who conducted and reported the original research cited in the book (both in the reference lists and the "Further Reading" sections of each chapter). Many multiauthored review articles are also cited, some of which are reports from the Cardiac Safety Research Consortium: thanks are expressed to all authors.

Finally, we thank our family members for their support during the writing of this book. JRT would like to offer special thanks to Mac, Charlie, and Sassy, who loved to lie on the piles of papers strewn all over his home office floor. In addition to providing delightful companionship during many hours of burning the midnight oil, they offered a multitude of excellent editorial suggestions with simple twitches of their whiskers before falling gently asleep and dreaming the dreams of very beautiful and erudite cats.

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Chapter 1

The Central Role of Cardiovascular Safety in Drug Development and Therapeutic Use

It is an unfortunate but immutable fact that no biologically active drug is free from the possibility of causing adverse reactions in certain individuals who are genetically and/or environmentally susceptible.

1.1 Introduction

The word "drug" has various connotations in everyday language. In this book, it refers specifically to pharmaceutical and biopharmaceutical molecules that are used to treat or prevent biological states of clinical concern. The term pharmaceutical drug typically refers to a small-molecule drug (around 20–100 atoms, with a molecular weight of less than 900 daltons), while the term biopharmaceutical drug refers to macromolecules, often a protein produced via the large-scale cultivation of microbial or mammalian cells, which are much larger. For example, the immunoglobulin G (IgG) antibody is around 25,000 atoms and has a molecular weight of approximately 150 kilodaltons (Azbio web site).

For a new drug to receive regulatory approval for marketing, regulators in respective geographical jurisdictions must decide that the drug has a favorable benefit–risk balance. This necessitates that the pharmaceutical or biopharmaceutical company requesting marketing approval for their drug must provide compelling evidence of the drug's therapeutic benefit and compelling evidence that it is acceptably safe. The term "acceptably safe" may initially seem strange, but it is appropriate. It is an unfortunate but immutable fact that no biologically active drug is free from the possibility of causing adverse reactions in certain individuals who are genetically and/or environmentally susceptible. When making marketing approval decisions, regulators therefore balance the therapeutic benefit provided by a drug with its toxicity. This concept is encapsulated by the term benefit–risk balance. Assessments of benefit are relatively straightforward, but assessments of toxicity are far from it, as will be seen throughout this book.

J.R. Turner et al., *Cardiovascular Safety in Drug Development and Therapeutic Use*, DOI 10.1007/978-3-319-40347-2_1

1.2 Drug Safety

The term drug safety is widely used when discussing the degree and extent of a drug's toxicity. Upon first examination, this term might also seem strange: what is actually being discussed can be better described as drug harm (Sect. 15.7 provides more detailed discussion on this topic). However, several reasons support our choice of the term drug safety. One of these is the nature of media coverage of reports of purported cardiovascular (and other) side effects of marketed drugs. The perception of a cardiovascular risk being associated with a marketed drug, whether or not the risk has been sufficiently well investigated to regard the risk as real, attracts enormous media attention. As Turner and colleagues (Turner et al. 2010) commented, "In the era of sensationalist, sound-bite coverage, clinical science sadly falls very low on the list of points to be covered in the allotted 30 s of television coverage." When a cardiovascular safety concern associated with a marketed drug is "identified," there is frequently a "torrent of recriminations" (Cobert 2007). In this context, the term drug harm would likely be incendiary, attracting even more emotive behavior and sensationalism to an area already fueled by far too much of both.

Such recriminations are almost always directed at the drug's sponsor (the company that developed and marketed the drug), and the consequences can be considerable, ranging from loss of reputation to a decrease of billions of dollars in market capitalization, even if the "identification" of a risk is subsequently refuted (a Case Study of such refutation is presented in Chap. 12). However, and perhaps increasingly so, recriminations can also be targeted at regulatory agencies. In addition to being in the best interests of patients, which is always the paramount consideration, doing everything possible to identify any degree of cardiovascular risk in preapproval trials is therefore also in the best interests of sponsors and regulators. Both of these stakeholder groups are cognizant of this, and in contemporary drug development, they work very closely together in this regard.

Given that the term drug safety is the one adopted throughout this book, it needs to be defined operationally. One relatively simple but nonetheless meaningful conceptualization of safety is as the inverse of harm: the less a drug's toxicity, the greater its safety (Durham and Turner 2008). Going a step further, a useful and widely adopted definition of drug safety in terms of benefit–risk assessment was provided by the US Food and Drug Administration's (FDA's) Sentinel Initiative (FDA 2008a):

> Although marketed medical products are required by federal law to be safe for their intended use, *safety does not mean zero risk*. A safe product is one that has acceptable risks, given the magnitude of benefit expected in a specific population and within the context of alternatives available.

When making a marketing approval decision, regulators make a benefit–risk decision at the public health level. That is, they have to answer this question: On balance, is this drug likely to do more good than harm in the entire population in the region under our jurisdiction with the condition of clinical concern? The drug must be considered to have a favorable benefit–risk balance to receive marketing approval.

A similar decision process occurs at the level of the individual patient once a relevant drug is approved: the physician and the patient must decide together that a particular course of pharmacotherapy has a favorable benefit–risk balance for the drug to be prescribed.

The process of benefit–risk estimation can be represented as follows (Turner 2010):

$$\text{Benefit-risk estimate} = \frac{\text{Estimate}\left(\text{probability and degree}\right)\text{of benefit}}{\text{Estimate}\left(\text{probability and degree}\right)\text{of harm}}.$$

In addition to considering harm, this representation makes clear that benefit must be considered as well. Therefore, while not the primary focus of this book, examples of statistical methodologies that facilitate assessment of benefit are presented in Chap. 4.

1.3 Notable Events Driving Assessments of Drug Safety and Efficacy

At the start of the twentieth century, there were no federal regulations in the USA to protect the public from dangerous drugs. Manufacturers were not required to provide evidence of a drug's safety, quality, or effectiveness before selling it. A series of Acts has transformed that environment into one in which compelling evidence of all three characteristics must be provided before a drug is approved for marketing. The US Pure Food and Drug Act of 1906, the first of several major consumer protection Acts, was intended to prevent the manufacture, transportation, or sale of adulterated, misbranded, or poisonous foods, drinks, and drugs. Governance of the Act was assigned to a division of the US Department of Agriculture that became the FDA in 1930.

The US Federal Food, Drug, and Cosmetics Act of 1938 (FFDCA) took consumer protection to the next level. While it had been under congressional discussion for several years, it was galvanized by the elixir sulfanilamide tragedy in which more than 100 people were fatally poisoned after ingestion of the elixir diethylene glycol, an ingredient used to dissolve sulfanilamide (see Schep et al 2009; Conrad et al. 2016). The fundamental requirement introduced by the FFDCA was provision of compelling evidence of a drug's safety at the time of application for marketing approval.

In Europe, the thalidomide tragedy spurred events that led to the United Kingdom's (UK's) Medical Act of 1968. Thalidomide was first marketed in 1956 in Germany for the treatment of insomnia and vomiting in early pregnancy. In 1961, a sizeable increase in the incidence of congenital birth defects was noted. These defects were typically an absence or reduction of the long bones of the limbs in the presence of normal or rudimentary hands and feet. The association of these

conditions with thalidomide was not recognized for several years after the drug was marketed, and several thousand babies in Europe were born with this congenital condition.

While public awareness of the events in Europe was a powerful motivator for congressional action for further drug law reform, as discussed in the next paragraph, the USA did not experience the same tragedy from the use of thalidomide. Having seen the reports from Europe, Dr Frances Kelsey, a newly appointed reviewer at the FDA, undertook considerable research and, as a result, took a firm stance against the drug's approval. In recognition of her diligence, she was awarded the President's Award for Distinguished Federal Civilian Service 2 months before further amendments to the FFDCA were signed in 1962.

Perhaps the most salient event in the regulatory process for new drug development was the passage of the Kefauver–Harris Amendments to the FFDCA, which were signed into law by President Kennedy in 1962 (see Turner 2012). Until these Amendments were signed, drug manufacturers were only required to provide compelling evidence that new products could be safely used before putting them on the market. The central novel requirements of the Amendments concerned the additional provision of compelling evidence of efficacy at the time of application for marketing approval. The Amendments were a powerful influence in the continued development of the randomized clinical trial, which is now considered to be the gold standard in providing compelling evidence of efficacy of a new drug. The more accurate term for this study design is the randomized concurrently controlled clinical trial, because a concurrent control treatment arm is a fundamental aspect of the trial's comparative nature: however, we will use the traditional nomenclature. The randomized clinical trial, discussed in more detail in Chap. 4, became the key methodology for providing the compelling evidence of efficacy required by the Amendments.

1.4 Cardiovascular Safety

Drugs that are indicated for cardiovascular conditions are expected to influence the appropriate component(s) of the cardiovascular system to generate their desired therapeutic benefit. For example, antiarrhythmic drugs are intended to influence the aberrant pattern of the heart's beating to return it to the normal pattern. Similarly, antihypertensive medications are expected to lower blood pressure. In contrast, drugs for noncardiovascular conditions, referred to in this book as noncardiovascular drugs, are not expected to influence the cardiovascular system. However, as noted previously, no biologically active drug is free from the possibility of causing adverse reactions. While some chapters focus on evaluations conducted during preapproval drug development to ensure to the greatest degree possible that a new drug does not carry an unacceptable risk of precipitating cardiovascular adverse reactions, discussions concerning postmarketing evaluations and discussions of the therapeutic use of marketed drugs are also provided.

Cardiovascular adverse drug reactions carry both short-term and long-term risks. For example, certain alterations in the heart's natural pattern of electrical activity can precipitate sudden cardiac death, while increases in blood pressure can play a role in the development of various cardiovascular conditions over long periods. The domain of cardiovascular safety is therefore of central importance in contemporary drug development. Four examples of such drug safety investigations, introduced here in turn, are discussed in subsequent chapters.

1.4.1 Proarrhythmic Cardiac Safety

The first goal of the field of proarrhythmic cardiac safety (often referred to simply as cardiac safety: see Turner and Durham 2009) is to determine whether a noncardiac drug has an unacceptable propensity to lead to the polymorphic ventricular dysrhythmia called torsades de pointes (torsades) in patients who may be prescribed the drug should it subsequently be approved for marketing. Such arrhythmogenesis can result in nonfatal dysrhythmias causing syncope (fainting), but on rare occasions it can prove fatal. The second goal is to remain alert to unexpected cardiac adverse drug reactions during its therapeutic use.

Proarrhythmic cardiac safety concerns led to the marketing withdrawal of various drugs in the UK and the USA from the late 1980s to the early 2000s. These included terodiline (indicated for urinary incontinence, withdrawn from UK and US markets in 1991), antihistamine terfenadine (withdrawn from the US market in 1998), and levacetylmethadol (indicated for opiate addiction, withdrawn from the UK market in 2003). Regulatory, scientific, and clinical interest concerning these marketing withdrawals led to the release in 2005 of two guidelines from the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): ICH S7B, which focuses on nonclinical assessments of relevance to the proarrhythmic liability of noncardiac drugs (ICH 2005a), and ICH E14, which addresses preapproval clinical assessments (ICH 2005b). ICH E14 introduced the Thorough QT/QTc (TQT) Study. An ICH E14 "Questions & Answers" document containing questions and associated answers was released in June 2008, a revised version containing additional questions and answers was released in April 2012, and a second revised version was released in March 2014. These documents provided additional guidance as experience was gained over time in the execution of the TQT study, a topic discussed in detail in Chap. 7.

A third revision, referred to in this book as ICH E14 Q&A R3, was released in December 2015 (ICH E14 Implementation Working Group 2015). ICH E14 Q&A R3 is likely to have considerable ramifications in the domain of preapproval clinical assessment of a drug's proarrhythmic liability. It makes it clear that a second form of assessment of a drug's proarrhythmic liability, exposure–response modeling, is an acceptable alternative to the TQT study. Chapter 8 discusses this topic. Chapter 9 then discusses the Comprehensive in vitro Proarrhythmia Assay (CiPA), an initiative investigating more sophisticated approaches to the nonclinical assessment of a drug's proarrhythmic liability (see Sager et al 2014).

1.4.2 Cardiovascular Safety Considerations in Oncology Drug Development and Therapeutic Use

It has long been known that many oncologic agents are cardiotoxic. However, when the best hoped-for outcome was keeping patients alive for a few extra months or years, the risk of cardiovascular disease at some indeterminate point in the future did not seem problematic to many patients from a benefit–risk perspective. The excellent news is that many individuals now live cancer-free for decades following cessation of treatment, but the corollary is that we need to pay very close attention to cardiotoxicity considerations.

Several considerations are pertinent here. First, during drug development, it is necessary to adapt proarrhythmic cardiac safety investigational methodologies because the cytotoxic nature of many oncologics precludes their being administered to healthy clinical trial participants in typical Phase I trials and a TQT study. Second, given the benefit these drugs provide in life-threatening illnesses, a greater degree of risk may be acceptable when granting marketing authorization than is acceptable for drugs indicated for less severe conditions. Third, heightened clinical awareness and patient care is needed. Although such therapy has proved very successful in many cases, with disease states going into remission and patients living for many years after cessation of treatment, cardiotoxicities can manifest themselves in different time scales: some appear relatively soon, while others can appear more than a decade later. Cardiovascular events of concern include cardiomyopathy leading to heart failure, cardiac dysrhythmias, thromboembolic events, and hypertension (Turner et al 2014). This topic is discussed in Chap. 10.

1.4.3 Blood Pressure Responses to Noncardiovascular Drugs

It has become clear in recent years that noncardiovascular drugs can affect blood pressure in an off-target manner by raising or lowering pressure or by negating the beneficial hypotensive effect of concomitantly prescribed antihypertensive drugs (Sudano et al 2010; Grossman and Messerli 2012; Sager et al 2013). In most cases, the increases in blood pressure are mediated by known mechanisms, including salt and water retention, activation of the sympathetic nervous system, inhibition of prostacyclin, and inhibition of vascular endothelial growth factor. In most instances drug-induced off-target blood pressure increases are relatively small, and the clinical relevance of these small and transient effects to symptomatology, morbidity, or mortality is not known because the subject has not been systematically studied (O'Brien and Turner 2013). However, effects of more immediate concern have certainly been documented: Grossman and Messerli (2012) observed that "severe hypertension involving encephalopathy, stroke, and irreversible renal failure have been reported." Off-target blood pressure responses have therefore garnered increasing scientific and regulatory interest in recent years. This topic is discussed in Chap. 11.

1.4.4 Cardiovascular Safety of Antidiabetic Drugs for Type 2 Diabetes

Formalization of this domain of cardiovascular safety can be traced to an FDA Guidance for Industry released in final format in December 2008 (FDA 2008b) and a subsequent Guideline released in final format by the European Medicines Agency (EMA) in May 2012 (EMA 2012). Both of these documents address the prospective exclusion of unacceptable cardiovascular risk associated with new antidiabetic drugs for the treatment of type 2 diabetes. The existence of an FDA general diabetes drug development guideline (FDA 2008c) allowed the FDA's new document to focus exclusively on cardiovascular safety, while the EMA's document addresses this topic as one component of an updated comprehensive guidance on multiple facets of diabetes drug development.

While the precise details of the FDA and EMA documents differ, the consequences are the same: in the vast majority of cases, a large cardiovascular safety outcome trial will need to be conducted to prospectively exclude an unacceptable cardiovascular risk, or liability, associated with a new drug. The name cardiovascular safety outcome trial conveys that the endpoints of interest are clinical outcomes as opposed to surrogate endpoints, such as blood pressure increases, which are taken to be indicative of increased cardiovascular risk but are not in themselves a clinical outcome. The outcomes most typically considered are the events comprising the major adverse cardiovascular event (MACE) composite endpoint, i.e., nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death. The number of outcomes in the drug treatment group is compared with those in the control treatment group, and a statistical analysis is conducted to determine whether or not the number of outcomes in the drug treatment group is unacceptably greater than the number in the control treatment group.

Cardiovascular safety outcome trials require very large numbers of participants. As an example, the SAVOR-TIMI 53 trial for saxagliptin employed 16,500 participants (Scirica et al. 2013). Such trials can take 5–7 years to conduct and can cost several hundred millions of US dollars. We previously expressed our concern that the new regulatory landscape generated by the FDA and EMA documents may prove to be a deterrent for some sponsors considering continued involvement in developing new drugs for type 2 diabetes (Caveney and Turner 2010): such an occurrence would likely have proved detrimental to patients, who on average need a new drug added to their treatment regimen every 3–5 years to maintain adequate control of blood glucose (EMA 2012). Fortunately, despite the added burden of bringing these drugs to market, new drugs continue to be developed. For example, at the time of writing this chapter, the following drugs have been approved in the USA since issuance of the FDA's December 2008 guidance: albiglutide, alogliptin, canagliflozin, dapagliflozin, exenatide extended-release, linagliptin, liraglutide, and saxagliptin.

In a 2014 paper published in the journal *Circulation*, Menon and Lincoff (2014) detailed ongoing cardiovascular outcome trials at the time of their paper's

preparation. After excluding the previously mentioned SAVOR-TIMI 53 trial that has now been completed, the total number of participants required for the remaining trials was around 122,500, a staggeringly large total. While access to the precise cost of each trial is not possible, it can safely be assumed that the total cost is several billion US dollars.

It is therefore of considerable interest to many stakeholders to determine the most expedient methodologies for satisfying the FDA and EMA requirements. An Expert Perspectives paper from the Cardiac Safety Research Consortium (CSRC: see Sect. 1.8) discussed clinical development strategies, operational issues, and statistical methodological issues in this regard (Geiger et al 2015). Going one step further, various professional organizations, including the CSRC, are exploring alternate ways of providing equally compelling evidence of the cardiovascular safety of new drugs for type 2 diabetes that may become components of regulatory landscapes in this area as they evolve in the future (Sager et al 2015). This topic is discussed in Chaps. 12 and 13.

1.5 Postmarketing Surveillance

In Part VI of the book, attention turns to postmarketing safety assessments. The importance of these assessments is captured succinctly yet powerfully by a quote from a report by the Institute of Medicine (IOM) of the National Academies entitled "The Future of Drug Safety: Promoting and Protecting the Health of the Public," which reads as follows (IOM 2007):

> The approval decision does not represent a singular moment of clarity about the risks and benefits associated with a drug – preapproval clinical trials do not obviate continuing formal evaluations after approval.

Chapter 14 therefore discusses a variety of topics, including clinical trials that are performed following a drug's marketing approval, various postmarketing safety surveillance strategies, and cardiovascular safety in clinical practice. Chapter 15 then provides discussion of a sample of other domains of drug safety: cardiovascular safety is a very important domain, but by no means the only safety domain. Topics include adherence to prescribed medication regimens, abuse of opioid medications, and safety aspects of precision medicine.

1.6 Clinical Research Methodology

This book discusses experiments involving human participants, also known as clinical trials. It is incumbent on all individuals conducting such research to gain a solid understanding of all aspects of clinical research methodology. This term is used as an overarching term to encapsulate study design, experimental methodology, operational execution, and statistical analysis. Not everyone needs to be an expert in all

of these components, but all clinical researchers should be well versed enough in areas outside their immediate expertise to appreciate all aspects of such research and, accordingly, to be able to communicate effectively with all collaborators.

1.6.1 Components of Clinical Research Methodology

The purposes of several key components of clinical research methodology can be summarized as follows (Turner 2012):

- Study design: designing a clinical trial to facilitate the collection of optimal data, i.e., unbiased and precise numerical representations of biologically important information that best answer the research question of interest
- Experimental methodology: considering and implementing all necessary procedures that, if executed correctly, allow the acquisition of optimal-quality data
- Operational execution: conducting all operational and experimental tasks correctly and therefore actually acquiring optimal-quality data
- Statistical analysis: describing, summarizing, analyzing, and interpreting the data collected to answer the research question

While they are listed separately here, these components ideally interact and integrate in a seamless manner.

1.6.2 The Discipline of Statistics

To those of you for whom the word "statistics" elicits feelings of mystery, threat, or irrelevance, it should be emphasized here that our discussions of statistics are couched in conceptual rather than computational terms. A conceptual understanding of the nature of several analyses of special interest in cardiovascular safety, most importantly the nature of the information they provide and the decisions that they facilitate, is essential to follow later discussions to the greatest advantage. To assuage any concerns you may have at this point, it may be helpful to think along the following lines. The discipline of Statistics (deliberately recognized in this context by the use of an uppercase "S" to distinguish it from individual statistics such as the arithmetic mean of a group of numbers) is simply a "way of doing business" that enables meaningful information to be collected and shared and to be done so according to a set of rules by which everyone agrees to abide. This agreement means that, when researchers have done everything correctly, everyone agrees to honor the results obtained. The discipline of Statistics therefore provides the structural architecture for drug development, including investigations of cardiovascular safety.

In the context of this book's discussions, Turner (2010) noted that the discipline of Statistics can be regarded as an integrated discipline that is important in all of the following activities associated with a clinical trial:

- Identifying a biologically important research question that needs to be answered.
- Deciding upon the design of the study, the experimental methodology that will be employed, and the numerical representations of biologically important information (data) that will be collected.
- Presenting the design, methodology, and data to be collected in a study protocol. This study protocol specifies the manner of data collection and addresses all methodological considerations necessary to ensure the collection of optimal-quality data for subsequent statistical analysis.
- Identifying the statistical techniques that will be used to describe and analyze the data in an associated statistical analysis plan, which should be written in conjunction (and concurrently) with the study protocol. (Sometimes protocols incorporate this information.)
- Describing and analyzing the data. This includes analyzing the magnitude of mean responses to the test drug and a comparator drug in conjunction with the variation in the data to see if there is compelling evidence that the drug is acceptably safe and effective. This process includes evaluation of the statistical significance of the efficacy results obtained and also evaluation of their clinical significance.
- Presenting the results of a clinical study to a regulatory agency in a clinical study report and presenting them to the clinical community in a journal publication. The latter topic is discussed in more detail in Sect. 15.7.

The contributions of the discipline of Statistics to drug development, including cardiovascular safety considerations, are therefore much richer than simply number crunching. Statistical considerations are the cornerstone of designing clinical trials capable of generating optimal-quality data whose appropriate analysis and interpretation form the rational basis of decision-making, both by the sponsor developing the new drug and the regulatory agencies that will determine whether or not the drug receives marketing approval in their respective jurisdictions. Certainly, calculations need to be performed during the statistical analysis of data collected during clinical trials: however, computers are supremely placed to do so, thereby allowing statisticians to focus on far more thoughtful issues.

1.6.3 Ethical Considerations and Responsibilities

Several fundamental ethical principles guide clinical trials, including clinical equipoise, respect for study participants, beneficence, and justice. These are summarized here in turn.

Clinical equipoise exists when all of the available evidence about a new drug does not show that it is more beneficial than an alternative and, equally, does not show that it is less beneficial. For example, to be able to conduct a clinical trial that involves administering a drug to some participants and a control treatment (sometimes a placebo and sometimes a comparator that is also biologically active)

to other participants, there cannot be any compelling evidence that the drug shows unacceptably greater or lesser efficacy than the control treatment or that it leads to unacceptably greater (in magnitude and or severity) side effects than the control treatment. When individuals agree to participate in a clinical trial, they do so with the understanding that all of the treatments in the trial are assumed to be of equal value. By the end of the trial, there may be compelling evidence that the investigational drug is acceptably safe and more effective than the control treatment, but the trial must be started with a good faith belief that the drug and the control treatment are of equal merit.

The principle of respect for study participants necessitates that investigators give potential participants all pertinent information about the study and then answer any questions they have. If a potential participant then agrees to participate voluntarily (i.e., he or she is not coerced in any real or implied manner), informed consent is obtained. This involves obtaining the individual's written permission (or the written permission of a parent or guardian) to participate in the study. It also necessitates protecting potential participants with possibly impaired decision-making capacity and maintaining confidentiality of all information obtained at every stage of the study.

The principle of beneficence requires that the study design is scientifically sound and that any risks of the research to be conducted are acceptable in relation to the likely benefits from the study (in terms of knowledge obtained that may benefit a large number of individuals). This applies not only to the investigational drug treatment arm but also to the control treatment arm, which may be a placebo. Being randomized to the placebo arm should not deprive patients of already available treatment in a manner that may result in worsening of their underlying disease.

The principle of justice requires that the burdens and benefits of participation in clinical trials are distributed evenly and fairly. Historically, populations that were easily and conveniently accessed by researchers, such as prison inmates, nursing home residents, and people with poor access to general health care, have been included in clinical trials when they should not have been. Vulnerable populations in which individuals may find it difficult to refuse participation in a study should not be deliberately chosen for participation in clinical trials when non-vulnerable populations would also be appropriate. The benefits of participation, such as access to potentially lifesaving new therapies, should be available to all, including those not historically well represented in the clinical research enterprise, such as women, children, and members of ethnic minorities.

In addition to these overarching tenets, all clinical researchers have ethical responsibilities that may not be as readily apparent. They also have an ethical duty to design, execute, analyze, and interpret the results of every trial in an optimal manner and to report the results with clinical decorum whenever and wherever they do so (in the media as well as at scientific conferences). From the scientific perspective, an inappropriate study design is incapable of answering a research question, no matter how carefully methodological and statistical questions are addressed. Similarly, the appropriate design will not provide optimal information if the research methodology is flawed or the appropriate statistical analysis is not performed. There is also

an ethical perspective pertaining to the use of optimal experimental research methodology. Individuals participating in clinical trials do so voluntarily with the understanding that their participation will provide information that is useful and generalizable to a much larger group of people. This is one of the "benefits" that must be weighed against the "risks" of their being exposed to a drug under development. If the clinical trial is conducted in such a manner that the data collected do not permit the best possible information to be obtained, the participants' expectations have been violated, an occurrence that is completely unacceptable. As noted previously, it is therefore incumbent on all researchers to gain a solid understanding of all aspects of clinical research methodology.

Derenzo and Moss (2006, p.4) captured the importance of ethical considerations in all aspects of clinical studies as follows:

> Each study component has an ethical aspect. The ethical aspects of a clinical trial cannot be separated from the scientific objectives. Segregation of ethical issues from the full range of study design components demonstrates a flaw in understanding the fundamental nature of research involving human subjects. Compartmentalization of ethical issues is inconsistent with a well-run trial. Ethical and scientific considerations are intertwined.

1.7 Biological Knowledge Is of Critical Importance

The word "clinical" in the terms clinical research and clinical trials alerts us to the tremendous importance of biological knowledge and considerations in drug development. The data that are collected during a trial are numerical representations of biologically important information. Clinical research and clinical trials investigate topics of clinical relevance, and clinical relevance is intimately related to biological relevance. The engine that drives new drug development is an unmet medical need, which is ultimately an unmet biological need. The goal of new drug development is to identify a biologically active compound that is acceptably safe, well tolerated, and useful in the treatment (or prevention) of patients' biological states of clinical concern (Turner 2010). This book's focus on drug safety means that we are primarily interested in off-target responses rather than the on-target responses of importance when evaluating therapeutic benefit: nonetheless, off-target responses are equally biological in nature.

Discussions in the following chapters address many topics that highlight the critical importance of biological knowledge and considerations. These include the following: a drug's progress through the body towards its target receptor and its possible interaction with off-target receptors (all receptors are biological structures); drug–receptor interactions and the resulting generation of biological signal that are often the result of a cascade of protein–protein interactions; metabolic pathways, biomarkers, genetics, and genomics; and the research methodology that is used to measure biological changes following drug administration, either via the assessment of surrogate endpoints or clinical outcomes. While the attention given throughout the book to study design, experimental methodology, operational execution, and statistical analysis is entirely appropriate, the importance of these topics lies with their roles in the prospective exclusion of unacceptable adverse biological responses.

1.8 The Cardiac Safety Research Consortium: The Power of Precompetitive Collaboration

The CSRC is a public–private partnership coordinated under a Memorandum of Understanding, signed in 2006, between FDA and Duke University. It employs collaborative, precompetitive exchanges of perspectives and information across multiple stakeholders to enhance new medical product development and advance the practice of medicine via a specific focus on cardiovascular safety. Virtually housed at Duke University's Clinical Research Institute, the Consortium's mission is to advance the regulatory science of cardiovascular safety assessment by bringing together stakeholders from industry, academia, and government in a neutral, precompetitive paradigm to share data and expertise and to support research into issues related to medical product cardiovascular safety. Its objectives include the following (see Finkle et al 2009; Krucoff 2011):

- Facilitation of focused, pragmatic research to inform regulatory processes with regard to cardiovascular safety.
- Development of knowledge and strategies intended to improve the evaluative sciences in relation to cardiovascular safety and product development.
- Development of expert consensus around common nomenclature, standards, and key definitions and the subsequent publication of White Papers in the *American Heart Journal* and Expert Perspectives in *Therapeutic Innovation & Regulatory Science*. These publications describe what is known and unknown and propose paths forward to address such knowledge gaps.
- Coordination of Think Tank Meetings and other programs and public forums for updates on, and open discussion of, multiple topics in the field of cardiovascular safety.

Finkle and colleagues (2009) provided introductory commentary on the series of White Papers in the *American Heart Journal*, noting that "The CSRC hopes that this series of articles will effectively engage stakeholders and cardiologists to foster safer medical products and provide approaches for increased efficiency in the development of medical products" (Finkle et al 2009). Additionally, CSRC members have published several papers in additional journals. As of finalizing this chapter, close to 30 papers have been published (Turner et al. 2016). Additional information can be found at the Consortium's web site, http://www.cardiac-safety.org/.

1.8.1 Collaboration with DIA: The Cardiac Safety Education Collaborative

As noted on its web site, the DIA (Drug Information Association) "was founded in 1964 by a group of 30 pharmaceutical professionals, medical writers and academicians who saw the need to facilitate communications and foster cooperative efforts among professionals working in health care industries primarily engaged in drug

development, medical communications, and health information" (www.diaglobal.org). Over the past half century, the DIA has operated as a fully independent organization that has grown into a highly respected international organization, thereby "providing educational and professional development opportunities for individuals working in the pharmaceutical and medical product development-related fields, as well as a global, unbiased forum for the exchange of information across multiple disciplines of programming and publications. These opportunities help facilitate the process of bringing life-saving medicines and health care technologies to the world." It is noteworthy that CSRC's and DIA's shared commitment to precompetitive collaboration and neutrality allows regulators and representatives from other governmental agencies across the world to participate in their activities.

Given shared interest in cardiovascular safety, CSRC and DIA have established the Cardiac Safety and Education Collaborative (CSEC). The CSEC is designed to leverage the unique and complementary capabilities of DIA and CSRC in a synergistic manner to provide educational offerings to the broad base of investigators, medical product companies, educators, regulators, and other policy makers involved in the development of medical products. One of the first joint events was a Webinar in November 2015 discussing the use of social media to garner information concerning cardiovascular adverse events, data that can be combined with those collected during traditional post-marketing surveillance to yield earlier, faster, specific, and actionable insights regarding prevention of adverse medical product events (Ghosh and Lewis 2015).

1.9 A Few Words About the Chapters in Part II and Part III

To make the book as self-contained as possible, and hence useful to readers with varying degrees of previous training in topics discussed, introductory material addressing biological and physiological considerations (Part II) and statistical considerations (Part III) has been included. The topics are not covered as they might be in comprehensive individual courses on these topics: rather, the chapters are specifically tailored to provide fundamental information that enables readers to follow the discussions about cardiovascular safety in subsequent chapters. This approach also enables those later chapters to be written without having to pause on multiple occasions to explain aspects of biology, study design, and statistical analysis. Some readers may already know much of the material covered in Parts II and III, and proceeding directly to the subsequent chapters may therefore be appropriate.

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Part II
A Primer of Biological and Physiological Considerations

Chapter 2

Drug Structures and the Biological Basis of Drug Responses

Drug-induced biological activity is generated in three-dimensional space: biological structures acting as drug receptors and the drug molecules that interact with them are three-dimensional entities.

2.1 Introduction

Drugs exert their therapeutic benefit by interacting with a target biological structure, generating a cascade of beneficial biological signaling and consequently changing a patient's biology for the better. Unfortunately, drugs can also lead to undesirable biological consequences, including adverse cardiovascular events. Before discussing the nature of these undesirable consequences and the methodologies for their prospective exclusion in subsequent chapters, it is appropriate to become familiar with the biological structures and systems activated by a drug. It is also useful to become familiar with the nature of the structure of a drug. This chapter therefore commences with a conceptual discussion of the structure of small-molecule drugs. It then discusses biological systems and the nature of interactions between biological structures and small-molecule drugs. Finally, it discusses drugs that are macromolecules: these discussions follow the introduction to biological systems since the nomenclature introduced there facilitates their description.

Biological considerations in this chapter are addressed from a pragmatic perspective and tailored specifically to suit current needs. In keeping with our goal of writing a self-contained book on cardiovascular safety, our discussions have been geared towards readers who will benefit most from them: readers who are already well versed in basic biology may prefer to progress directly to the next chapter.

2.2 Small-Molecule Drugs: New Molecular Entities and Drug Molecules

A molecule is the essence of a substance, the smallest unit of that substance that still retains the substance's chemical identity. The atoms within a molecule can be conceptualized as being grouped into various molecular components called functional groups. A common functional group in acidic molecules, for example, is the

J.R. Turner et al., *Cardiovascular Safety in Drug Development and Therapeutic Use*, DOI 10.1007/978-3-319-40347-2_2

carboxylic acid group, represented in the language of atoms as "COOH." This functional group consists of a carbon atom, two oxygen atoms, and a hydrogen atom. Functional groups determine the chemical and physical properties of molecules.

Drug-like molecules possess certain characteristics. For example, they have a relatively low molecular weight and possess one or more functional groups that are held together on a structural framework or backbone. This backbone needs to be relatively rigid to ensure that the shape of the molecule does not alter too much. The functional groups are therefore positioned in three-dimensional space in a specific geometrical array and are available to interact with drug receptors within the body. The term drug-like molecule refers to a molecule that could theoretically be a match for a site on a receptor: once it is known that the molecule will bind (interact) with a specific receptor site, the term drug molecule is used.

A drug molecule can be regarded as a "collection of molecular fragments held in a three-dimensional arrangement that determines and defines all of the properties of the drug molecule" (Nogrady and Weaver 2005). These properties include physiochemical, shape and stereochemical, and electronic properties. They are important in determining whether or not a drug molecule that is administered to an individual will actually reach the microenvironment of the drug target and, if it does, whether or not it will interact with the drug target successfully.

Nogrady and Weaver (2005) discussed the influences of these properties. Physiochemical properties impact a drug's solubility and pharmacokinetic characteristics, influencing the drug's ability to reach the region of the body in which the drug target is located, which can be a long way from the site of the drug's administration (oral administration is common, but by no means the only way a drug can be administered). Shape and stereochemical properties affect the pharmacodynamic phase of drug action and influence the drug's interaction with its target receptor. These properties describe the structural arrangement of the drug molecule's constituent atoms and influence the molecule's final approach towards the target receptor. Electronic properties also affect the pharmacodynamic phase of drug action. The electronic properties of a molecule are governed by the distribution of electrons within the molecule and give each region of a molecule a positive, negative, or neutral charge. These properties determine the exact nature of the binding interaction that occurs between the drug and its target receptor and the degree to which the interaction is energetically favorable. The energetic exchange that occurs between the drug molecule and the receptor determines the strength of the biological signal that is generated. It is this signal that governs the pharmacological (biological) effects of the drug.

2.2.1 Pharmacophores and Toxicophores

Wermuth (2006) discussed the terms pharmacophore and toxicophore. A pharmacophore is a concept used to account for the common molecular interaction capacities of a group of compounds towards their target receptor. It can be considered as

the highest common denominator of a group of molecules exhibiting a similar pharmacological profile and which are recognized by the same target receptor. It describes the essential (steric and electronic) function-determining points necessary for an optimal interaction with a relevant target receptor. Once the drug molecule enters the microenvironment of the target receptor, it is necessary that the geometry of the molecule precisely matches the geometry of the receptor site on the target receptor molecule. The pharmacophore therefore needs to be spatially and geometrically positioned consistently as the drug molecule approaches the target receptor.

At this point, it is worth introducing stereoisomers. These are isomeric molecules that have the same molecular formula and hence the same sequence of bonded atoms. However, they differ in the three-dimensional orientation of their constituent atoms. For example, consider the example of the antiarrhythmic drug sotalol. Both d-sotalol and I-sotalol isomers affect I_{Kr} that influences cardiac repolarization, but only the I-isomer has beta-blocking effect. Another example is warfarin. The S-isomer is three to five times more potent than the R-isomer, and they are metabolized by different cytochrome pathways, an influence that contributes to variable response and toxicity between batches of the drug and ethnic populations.

In a similar manner, and of greater relevance for this book's discussions, a toxicophore is conceptualized as an assembly of geometrical and electronic features of a different functional group of atoms in the drug molecule that interacts with a nontarget receptor and elicits an unwanted biological response or side effect. There is no meaningful structural or molecular difference per se between a pharmacophore and a toxicophore: the names are determined by intent, with a pharmacophore intended to interact with the target receptor, and a toxicophore unintentionally interacting with an off-target receptor and leading to an undesirable effect. (There are instances where a drug being developed for use in particular disease has demonstrated unanticipated off-target effects that have serendipitously been desirable effects for another disease, and the drug became marketed for that indication.)

2.2.2 Drug Discovery and Drug Design

Traditionally, the terms drug discovery, nonclinical development, and clinical development have been used to describe the process of research conducted to bring a new drug to marketing approval. Along with postmarketing surveillance, they are components of lifecycle drug development. Over the course of human history, many pharmacologically active agents were naturally occurring chemical substances, and discoveries of their medicinally beneficial properties were serendipitous rather than deliberate. As the pharmaceutical industry was formed, the process of drug discovery involved the evaluation of many molecules in a systematic manner to determine those with interesting pharmacological characteristics. It was quite possible that hundreds (if not thousands) of potential drug candidate molecules would be tested for pharmacodynamic action in what was a very laborious process.

More recently, as biomedical science has advanced rapidly and knowledge of molecular chemistry and molecular biology has increased dramatically, small-molecule drug discovery has become more driven by technology. The starting point in recent small-molecule drug development is often knowledge of the molecular structure of the drug's target receptor. Given this knowledge, molecular technologies are utilized to discover a drug whose molecular structure is appropriate to facilitate the desired pharmacological effect. Additionally, the term drug design has become common. Drug design is concerned with modifying the structure of an existing chemical molecule in specific ways, including modification of its pharmacokinetic profile or synthesizing a related new chemical molecule specifically for its pharmacological benefit.

As Nogrady and Weaver (2005) observed, the interdisciplinary science of medicinal chemistry provides "a molecular bridge between the basic science of biology and the clinical science of medicine." It focuses on the discovery/design of new molecular entities, their optimization, and their development as useful drug molecules for the treatment of disease. The authors also provided a comprehensive definition of a useful drug. A useful drug molecule has the following properties: it is acceptably safe; it is efficacious for the disease or clinical condition of concern; it is well tolerated; it can be manufactured in sufficiently large quantities by processes that can comply with all necessary regulatory oversight and that are financially viable for the sponsor; it can successfully navigate all necessary regulatory oversight, including those that govern nonclinical investigations and clinical trials, and be approved by regulatory agencies for marketing; and it can be successfully marketed and therefore be prescribed by clinicians (Nogrady and Weaver 2005).

With regard to the optimization of new molecular entities, there are three considerations: optimizing therapeutic benefit, minimizing toxicity resulting from the molecule's interaction with nontarget receptors, and, at the same time, optimizing pharmacokinetic properties such that the drug reaches its target receptor satisfactorily. Contemporary drugs are typically foreign substances, or xenobiotics, and the body therefore attempts to break them down as efficiently as possible. Therefore, regular short-term (perhaps one tablet a day for 7–10 days for an antibiotic) and long-term (perhaps one tablet a day for many years for an antihypertensive medication) administration is typically necessary.

Modern computing techniques are increasingly being used in drug discovery and design. Two recent trends have facilitated this paradigm shift. First, the phenomenal growth in information from molecular biological studies provides the pharmaceutical industry with tremendous opportunities to capitalize on this information in the development of new drugs. This includes a knowledge of how genetic material codes for the production of proteins, knowledge of the structure and function of proteins, how proteins create metabolic pathways, and how environmental factors affect the phenotypic expression of a person's genotype to create a unique individual human being (even in the cases of identical twins and other identical multiple births) with a unique set of metabolic pathways.

The second trend is a tremendous advancement in computing systems (often sophisticated networks, or clusters, of relatively small computers rather than

hugely powerful individual machines). The combination of advances in these areas has facilitated the development of bioinformatics and cheminformatics, highly computational fields that deal with storing and communicating the ever-increasing amount of molecular biological and chemical data available.

Historically, in vitro and in vivo testing has been the mainstay of evaluating a drug molecule's action before proceeding to clinical trials. The advent of tremendous computing power has changed many aspects of drug discovery and development, facilitating another approach known as in silico testing. Before a molecule is synthesized, extensive computer modeling takes place in an attempt to identify a molecular structure that would likely have a high probability of achieving the desired interaction with a target receptor. In silico development focuses on many aspects of the molecule, including its ability to reach the region of the drug receptor, its ability to approach and dock (bind) with the receptor, and the precise nature of the binding interaction with the target receptor. Of considerable relevance to later discussions in this book is that this field is also concerned with binding interactions with nontarget receptors.

Knowledge of the structure of the receptor macromolecule now permits research scientists to adapt the approaches of computer-assisted design to create the field of computer-assisted molecular design (CAMD). In combination with the disciplines of bioinformatics and cheminformatics, it has become possible to design lead compounds from scratch that are probabilistically well suited for further development and optimization. CAMD facilitates in silico three-dimensional docking experiments, i.e., simulations of potential drug molecules docking with receptors. The results of these experiments can identify a potentially safe and efficacious drug molecule relatively more easily, less expensively, and very much more quickly than other approaches in drug discovery.

As a lead compound is optimized, enhancing the features of the pharmacophore to elicit a more energetic therapeutic interaction with the receptor is desirable, as is modifying toxicophores to lessen or eliminate side effects. In addition to these pharmacodynamic and toxicodynamic considerations, pharmacokinetic considerations need to be addressed. The goal in this case is to modify the metabophore (the functional group of atoms in the drug molecule responsible for its pharmacokinetic properties) where possible to minimize the drug's metabolism in the liver and its rapid excretion by the kidneys, thereby giving the molecule a greater chance to reach its target receptor and exert its desired pharmacodynamic effects.

2.2.3 Structural Molecular Engineering: A Case Study

In combination with in silico modeling, structural molecular engineering offers the possibility of creating an optimized molecule by engineering desirable characteristics into and engineering undesirable characteristics out of the lead compound molecule. From our perspective, interest in structural molecular engineering lies with "engineering cardiotoxicity out of the molecule" to the greatest extent possible by

removing or functionally disabling toxicophore(s) that lead to undesirable cardiovascular effects while maintaining the molecule's optimal therapeutic and metabolic qualities.

Engineering out toxicophores can be considerably harder than engineering in pharmacophores, especially at the beginning of the process. While the target receptor is known, there is an enormous range of possible nontarget receptors. Some functional groups on a drug molecule may be known to comprise a toxicophore that should be avoided when designing any new drug. However, there remains the constant possibility that a functional group on a new molecule will react with a known nontarget receptor in an unexpected and undesirable manner or will interact in an undesirable manner with a previously unknown receptor. It is likely that engineering out toxicophores can be more readily achieved when the mechanism of action of a specified adverse reaction is known and is also separable from the mechanism of action of the intended response. This may be achieved by either limiting drug access to the location of the off-target receptor or by increasing the drug specificity for the on-target vs. off-target receptor (see Turner and Durham 2009).

An informative example is provided by the work of Fernández and colleagues (Fernández et al 2007). As will be seen in Chap. 10, many oncologic drugs are cardiotoxic, and considerable care is taken in the drugs' development and also their therapeutic use. Imatinib is a small-molecule drug that is a protein–tyrosine kinase inhibitor that inhibits the bcr-bl tyrosine kinase, and it also inhibits the receptor tyrosine kinases for platelet-derived growth factor (PDGF) and stem cell factor (SCF), c-kit, and inhibits PDGF- and SCF-mediated cellular events. The drug's specificity facilitates its treatment of chronic myeloid leukemia, where its target is the bcr-abl kinase, and also a proportion of gastrointestinal stromal tumors (GISTs), where its target is the c-kit kinase. However, it also has cardiotoxic effects traceable to its impact on the c-abl kinase. The researchers therefore engineered a "modification to imatinib that hampers Bcr-Abl inhibition; refocuses the impact on the C-Kit kinase; and promotes inhibition of an additional target, JNK, a change that is required to reinforce prevention of cardiotoxicity" (Fernández et al 2007). Imatinib was thus reengineered as an agent to treat GISTs with reduced cardiotoxicity.

2.3 A Brief Introduction to Biopharmaceuticals

The term biopharmaceutical was originally coined to define "therapeutic proteins produced by genetic engineering, rather than by extraction from normal biological sources" (Levine 2006), although the term now embraces a wider range of therapeutic interventions. The majority of approved biopharmaceuticals are proteins. Proteins are one of the topics discussed in this chapter as we provide a fundamental explanation of the biological basis of drug responses. Accordingly, additional discussion of biopharmaceutical drugs is provided in Sect. 2.12 since useful nomenclature and concepts will have been introduced by then.

2.4 Individual Variation in Responses to Drugs

One of the greatest challenges in pharmaceutical medicine is that all patients do not respond in the same manner to the same drug, a phenomenon called individual variation. When a drug is administered to different patients for whom it is appropriate as determined by the best diagnostic techniques currently available, many of these patients will safely experience a therapeutic benefit. However, there are other possible outcomes that may be experienced by relatively small numbers of patients:

- A patient may not show a beneficial therapeutic response. Increasing the dose may lead to a beneficial response in some cases.
- A patient may show an undesirably excessive therapeutic response (e.g., high blood pressure being reduced by an undesirable extent by an antihypertensive medication, leading to the patient becoming hypotensive instead of normotensive). A lower dose of the same drug may work well in some cases. Of interest in this scenario, the unwanted response is the result of excessive activation of the target biological structure, and hence the mechanism of action of the unwanted response is understood: this is not so easy to identify for other adverse drug reactions.
- A patient may show a relatively serious adverse drug reaction that result from the drug's interaction with an off-target receptor.

An understanding of the causes of individual variation in drug response requires knowledge of their biological underpinnings. This knowledge and pursuant understanding is being continuously enhanced by tremendous advances in molecular biology. Molecular biological aspects of drug responses are discussed later in the chapter, but first an overview of some basic biology is appropriate.

2.5 Deoxyribonucleic Acid

The acronym DNA is so well known that it is often used without reference to its full name, deoxyribonucleic acid. However, despite the ubiquity of the acronym, DNA's nature and function may be less well known to some readers. Since genetics play an extremely influential role in both therapeutically beneficial and adverse drug responses, it is appropriate to discuss DNA at this point in the chapter.

DNA is a macromolecule. Each word in its name is descriptive of its nature. Ribose is one form of sugar, along with glucose, fructose, sucrose, and others. The prefix "deoxy-" (the "D" in DNA) specifies a ribose that has lost one of its oxygen atoms at a specific site in the molecule. Nucleic acids (the "N" and the "A" in DNA) are a group of complex compounds comprised of carbohydrates, purines, pyrimidines, and phosphoric acid. Nucleic acids are found in all living cells.

2.5.1 Bases, Nucleotides, and Polynucleotide Strands

Each DNA macromolecule contains many copies of four bases, known as adenine ("A"), guanine ("G"), thymine ("T"), and cytosine ("C"). Each of these is a molecule in its own right, comprised of carbon, hydrogen, oxygen, and nitrogen atoms. These four bases can be meaningfully placed into two categories: pyrimidines, comprising thymine and cytosine, and purines, comprising adenine and guanine. Pyrimidines are chemical structures that are composed of one ring, and purines are chemical structures composed of two rings. Purines and pyrimidines can join together (bond) with a deoxyribose molecule that also contains a phosphoric acid group. The combination of each of the four bases (A, G, T, and C) with a deoxyribose molecule leads to the formation of four nucleotides. There are two pyrimidine nucleotides, thymine and cytosine, and two purine nucleotides, adenine and guanine. Being ring chemical structures, these nucleotides are relatively "flat," allowing them to stack up in a compact fashion. This characteristic makes the DNA macromolecule very strong. The planar geometry of individual nucleotides, however, is in marked contrast to the eventual three-dimensional shape of DNA.

Polynucleotide strands are made up from hundreds of thousands of individual nucleotides linked together. The nucleotides in a polynucleotide strand are combined in a specific manner. The forces that hold atoms, and hence molecules, together are called bonds, and bonds occur between specific atoms in specific ways. Nucleotides in a strand are held together by bonds between the sugar component of one nucleotide and the phosphate component of the other nucleotide. Since each nucleotide has both a sugar component and a phosphate component, it can bond to one nucleotide "above" it and another nucleotide "below" it, allowing a polynucleotide chain to be formed.

2.5.2 The Double Helix and Replication

Each DNA macromolecule is comprised of two strands of nucleotides that are attached together. This molecular structure and the ensuing molecular geometry of DNA lead to its characteristic double helix nature.

Once formed, strands of DNA like to be matched with, and attached to, another strand. The process of matching and attaching is nonrandom and governed by the following rules: an adenine base can only be matched with and attached to a thymine base and a guanine base can only be matched with and attached to a cytosine base. The term "complementary bases" reflects this arrangement: each of the four nucleotide bases has a complementary base to which it becomes attached. The consequence of this is that, once the sequence of nucleotides in one strand is known, the sequence of nucleotides in the other strand is also known.

Replication is the process that starts with the two polynucleotide chains that comprise a DNA molecule splitting apart from each other. Each then becomes

reattached to molecules that form a new partner, and the new partner is an exact copy of the original partner. This occurrence is governed by the complementary bases rule just described, i.e., the facts that adenine only binds with thymine and guanine only bonds with cytosine. Therefore, replication generates two precise copies of the original DNA macromolecule. These two copies can then replicate and result in four copies of the original. The exponential nature of replication means that one DNA macromolecule can produce an extremely large number of copies of itself, enough to form an entire organism.

2.6 Transmission Genetics and Molecular Genetics

Genetics, itself a relatively young science, is concerned with how traits are passed from one generation to the next. Since the advent of genomics, a more recent and hence even younger science, the term transmission genetics has come to represent what had previously been simply called genetics. The mathematics of transmission genetics were first described by Mendel in 1866 following his experiments with pea plants. It was shown that knowledge of certain phenotypic characteristics in the "parents" could be used to accurately predict phenotypic characteristics of the "offspring," but at that time, there was no biological knowledge of the exact nature of the "units of inheritance."

The more recent study of genes themselves is called molecular genetics. The focus of molecular genetics includes the physical and chemical structure of DNA. The information contained within our DNA codes for all of our individual characteristics. This includes eye color, blood type, susceptibility to disease, and, of particular relevance in this book, likely responses to drugs. When molecular genetic investigation expands from studying individual genes to studying the entire complement of the genome, the term genomics becomes appropriate.

2.6.1 Morgan's Research Employing Drosophila melanogaster

Genetic experiments using *Drosophila melanogaster*, the fruit fly, were first conducted in 1901 at Harvard University but were taken to the next level at Columbia University by Morgan starting in 1907 (see Watson 2004). The fruit fly has marked advantages for use in transmission genetic research: they are abundant in nature, and they are easily fed and accommodated. Moreover, they are prodigious reproducers. They have a generation time of 10 days, and females produce around 300 eggs each (of which half are female). In the space of a single month (three generation times), a single fruit fly couple can lead to 150 (half of 300) times 150 times 150 flies, i.e., over 3 million flies (Watson 2004).

Table 2.1 Approximate genomic data for humans and other organisms of interest

Organism and date genomic data obtained	Size of genome (base pairs)	Number of genes	Percentage of genes shared with humans
Humans (2004)	3 billion	20–25,000	(100 %)
Chicken (2004)	1 billion	20–23,000	60 %
Dog (2003)	6 billion	18,000	75 %
Fruit fly (2000)	165 million	14,000	50 %
Mouse (2002)	2.5 billion	30,000	80 %
Rat (2004)	2.75 billion	22,000	80 %

Adapted from Palladino (2006)

Since there was no current knowledge of established genetic differences in 1907, it was hard for Morgan to know where to start. As Watson (2004, p. 13) commented, "you cannot do genetics until you have isolated some distinct characteristics to track through the generations." A search for mutant genes was therefore started. Mutant genes, now more appropriately referred to as abnormal variant genes, are variations from the normally occurring genes, which are called normal variants. Abnormal variants can lead to distinct characteristics. This search led to the discovery of some flies with white eyes (the normal color being red). This gene was therefore named white.

The work of Morgan and his colleagues laid the groundwork for the Human Genome Project. While it may initially seem a stretch to move from studying genes in fruit flies to studying genes in humans, Table 2.1 makes this very meaningful extension much more readily appreciated.

Twenty or so years ago, it was widely thought that the human genome may contain upward of 100,000 genes: given the complexity of human biology and behavior, it seemed reasonable (if somewhat arrogantly so) to think that humans would have a substantially larger number of genes than other species. However, following the completion of the Human Genome Project, current estimates are in the 20–25,000 range (with the most authoritative perhaps closer to the lesser figure). As can be seen in Table 2.1, the numbers of genes for several other organisms of interest are strikingly similar to the number of genes for humans. Studying the genomes of these other organisms (particularly the mouse) is advancing understanding of the human genome. Importantly, individual genes of interest in this book are preserved to a great degree across different species.

2.7 Human Genetic and Genomic Considerations

Human DNA contains approximately three billion base pairs, but our 20–25,000 genes are comprised of only a small percentage (less than 5 %) of these base pairs. That is, less than 5 % of the human genome codes for proteins: the rest is noncoding and comprises long stretches of base pairs that are often repeated. As Watson (2004, p. 197)

noted, "protein-coding regions are but strings of As, Ts, Gs, and Cs embedded among all the other As, Ts, Gs, and Cs of the genome—they do not stand out in any obvious way." To make things even more difficult when locating genes, the base pairs that comprise a gene are not arranged in an uninterrupted linear sequence: there are noncoding sequences in between the coding sequences that together form the gene. Up until the mid-1970s, it had been generally accepted that genes existed as continuous segments within a DNA molecule. This view changed radically with the discovery in 1977 that, in higher organisms with eukaryotic cells (cells that have an outer membrane and additional membranes within the cell that surround the cell's nucleus and other intracellular organelles), an individual gene can comprise multiple DNA segments separated by chunks of noncoding DNA. This work led to researchers being awarded the 1993 Nobel Prize in Medicine.

An elegant editing process called RNA splicing (RNA is the acronym for ribonucleic acid, a molecule that shares many characteristics with DNA) removes these noncoding chunks of genetic material and connects together the relevant segments to create messenger RNA (mRNA). mRNA then ensures that amino acids are successfully made. Amino acids are joined together in various sequences to make proteins. Proteins are therefore made from the genetic instructions coded in the DNA molecule.

Noncoding sequences are called introns. A typical human gene has eight introns that lie between the coding sections, called exons, while the dystrophin gene, the largest gene found in nature, is spread across approximately 2.4 million base pairs (2.4 Mb) and is comprised of 87 exons (National Institutes of Health web site).

2.7.1 Proteins, the Proteome, and Proteomics

Genes code for proteins. That is, they contain the information that enables a sequence of amino acid residues to be joined together to form a protein. The naturally occurring amino acids are listed in Table 2.2. When a gene's protein is manufactured, the gene is said to be expressed. Gene expression involves genes being translated into mRNA intermediates, and these intermediates then being translated into proteins, as noted in the previous section.

One aspect of gene expression that facilitates the complexity of life in higher organisms is the fact that a given gene can yield many different proteins, not just the single protein that is "classically" associated with that gene. The processes of alternative splicing and posttranslational modification make this occurrence possible. As noted in the previous section, the term splicing is used when the different exons along a section of DNA that comprise a gene are joined together once the introns separating these coding sections have been removed. Usually, exactly the same set of exons is joined together to form the gene that produces a specific protein. Alternative splicing occurs when slightly different set of exons are spliced together, resulting in the creation of a different protein.

Table 2.2 Naturally occurring amino acids

Alanine	Glycine	Proline
Arginine	Histidine	Serine
Asparagine	Isoleucine	Threonine
Aspartic acid	Leucine	Tryptophan
Cysteine	Lysine	Tyrosine
Glutamic acid	Methionine	Valine
Glutamine	Phenylalanine	

As noted previously, only 20 amino acids are encoded genetically. Proteins (polypeptide chains) are assembled from these amino acids. The term posttranslational modification refers to biochemical changes that are made to the proteins after they have been produced. These modifications, which may be permanent or easily reversible (Glitz 2006), include glycosylation, hydroxylation, acetylation, phosphorylation, methylation, iodination, and sulfonylation. The most common protein posttranslational modification, glycosylation, involves the enzymatic attachment of sugars to the amino acid: approximately 50 % of proteins have sugars attached (Murray 2006). The number of proteins in the human proteome, the putative collection of all proteins, is therefore considerably larger than the number of genes in the genome. This phenomenon, as noted previously, is the result of "the simple although not widely appreciated fact that multiple, distinct proteins can result from one gene" (Holmes et al. 2005). Hence, the 20,000–25,000 human genes can produce many more proteins (estimates range upward of one million). Augen (2005) noted that this occurrence makes each person's totality of metabolic pathways unique, a phenomenon that can influence drug responses.

2.7.2 The Structure of Proteins

The word protein derives from the Greek word proteios, meaning "of first importance." Wishart (2005, p. 224) commented that "no other class of molecule exhibits the variety and irregularity in shape, size, texture, and mobility than can be found in proteins." Proteins are described using a model comprising primary, secondary, and tertiary structures. The primary structure represents the sequence of a protein, the string of amino acids that comprise it. The individual amino acids in this chain are termed residues, and these residues are joined together by peptide bonds to form chains. This string of amino acids is shapeless and is not biologically active. Secondary structures are formed by short stretches of residues. These substructures make up sequentially proximal components of proteins, and they have shapes. A complex combination of attractive and repulsive forces between close and more distant parts of the structure affects the resultant shape of secondary structures, and predicting secondary structure from knowledge of the linear amino acid sequence alone remains a tremendous challenge. The tertiary structure addresses the overall three-dimensional structure of the protein, which represents the spatial packing of secondary structures (Ofran and Rost 2005).

Two general properties of proteins are of direct relevance to drug responses. First, once a protein is formed, it does not exist as a linear chain of its constituent amino acids: rather, it folds into very complex geometries. Second, any change to any part of the structure of a protein may have an impact on its biological activity (Thomas 2003). Proteins can comprise hundreds of amino acids, and changes in an amino acid that is a long way from the active site of the protein in terms of its function can exert a major influence on that function. The tremendous diversity in proteins, and their specificity of shape and electrical charge, may be the reason for the evolution of their role as receptors.

2.8 Receptors

Most drugs exert their influence by interacting with specific macromolecules, often located in the surface membrane of a cell, in ways that alter the macromolecules' biochemical or biophysiological activities. This idea, which is more than a century old, is embodied in the term receptor. A receptor is regarded as the component(s) of a cell or organism that interacts with a drug and initiates the chain of biochemical events leading to the drug's observed effects (Bourne and von Zastrow 2004). Conceptually, receptors contain sites to which a functional unit on a drug molecule can attach; the three-dimensional shape of the functional unit is a match for the three-dimensional structure of the receptor site. The receptor concept has proved extremely useful in molecular biology for explaining many aspects of biological regulation, and receptors have become a central focus of investigation in the areas of pharmacodynamics and the molecular basis of drug actions, both on-target and off-target.

The receptor concept, therefore, has important practical consequences for the development of new drugs (Bourne and von Zastrow 2004). Receptors largely determine the quantitative relations between the concentration of a drug in the body and its pharmacological effects, and they are responsible for the selectivity of a drug's action. The molecular size, shape, and electrical charge of a drug determine whether and with what affinity (i.e., how strongly) it will bind to a particular receptor. Receptors mediate the actions of both pharmacological agonists and antagonists. Agonists activate the receptor to produce a physiological signal as a direct result of binding to it. Antagonists bind to a receptor but do not activate a signal. However, this binding has a very important consequence: other drugs or endogenous compounds that could have interacted with the receptor and caused a physiological signal are no longer able to do so. Antagonists, therefore, interfere with the ability of an agonist to activate the cell.

2.9 Cells and Cell Membranes

Devlin (2006) discussed the origins of cellular life. Initially, the elements carbon, hydrogen, oxygen, nitrogen, sulfur, and phosphorus formed simple chemical compounds. These compounds included water (represented as H_2O, indicating a

molecule incorporating two hydrogen atoms and one oxygen atom) and organic molecules, i.e., molecules that include the element carbon. Further developments led to increasing biological sophistication. As Devlin (2006, p. 2) commented:

> With continued formation of ever more complicated molecules, the environment around some of these self-replicating molecules became enclosed by a membrane. This development gave these primordial structures the ability to control their own environment to some extent. A form of life had evolved, and a unit of three-dimensional space, a cell, had been established.

No matter how complex an organism, the cell remains the basic unit of life. Organisms of interest in this book comprise eukaryotic cells. The plasma membrane fulfills two functions: it keeps the cell's overall internal environment relatively stable so that the cell can conduct its multiple functions and it allows interaction with the variable extracellular environment. The additional membranes that surround the cell's nucleus and other intracellular organelles create distinct cellular compartments with different environmental conditions within the cell's overall environment. These additional membranes effectively create and protect multiple intracellular environments in which different chemical reactions that require different environmental conditions can occur simultaneously (Devlin 2006).

Cell membranes consist of lipids and proteins. Every membrane possesses a different set of proteins, with plasma membranes comprising up to 100 proteins (inner membranes may have considerably less) (Murray and Granner 2006). Major functional molecules embedded within the plasma membrane of particular interest in this book include various protein structures: ion channels; receptors for endogenous molecules (molecules originating inside the body), including chemical messengers; receptors for exogenous molecules (molecules originating outside the body), including drugs; and enzymes. Ion channels (discussed shortly) facilitate the translocation of ions across membranes, and receptors interact with both small and large molecules. Enzymes act as catalysts for biological reactions, making it much easier for them to occur.

2.10 Ions and Ion Channels

Water is a major constituent within cells. Devlin (2006, p.4) noted that "Substances required for the cell's existence are dissolved or suspended in water. Life on earth exists because of the unique physiochemical properties of water." Water constitutes approximately 60 % of the human lean body mass, including both intracellular and extracellular fluid (Murray and Granner 2006). When molecules dissolve in water, they exist as ions, positively and negatively charged particles related to the atoms that comprise the molecule. For example, common table salt is the molecule called sodium chloride. Each molecule is comprised of one sodium atom (Na) and one chlorine atom (Cl). When salt is dissolved in water, two ions are formed: a positively charged sodium ion (Na^+) and a negatively charged chlorine ion (Cl^-). These ions are called electrolytes since their electrical charges make it possible for them to conduct electric currents.

Schultz (2006, p. 358) noted that "Structured molecular complexes of multiple protein subunits are common in biology." Ion channels are a very good example of such molecular complexes. Ion channels located in plasma membranes are known as transmembrane proteins since they permit the translocation of ions from one side of the membrane to the other. These ion channels have a multi-subunit structure that facilitates their function: these subunits include α-subunits and β-subunits. The transmembrane domains of many transmembrane proteins are known as α-helix subunits. Multiple α-helix subunits can be organized to form a channel, or pore, through which ions can flow from one side of the membrane to the other. Other forms of subunits, e.g., β-subunits, do not contribute to the structure of the central pore but are nonetheless important in providing "stabilizing influences" that allow the central pore to perform its function.

Since ions carry electrical charges, ion channels facilitate electrical signals in various excitable cells, including cardiac muscle (myocardial) cells, by permitting ions to flow from one side of a membrane to the other through the central pore created by the protein complex comprising the ion channel. The propagation of a biological signal results from the fact that the movement of ions through ion channels changes the electrical gradient between the cell's intracellular and immediate extracellular environment.

Certain properties of ion channels are of particular relevance in the context of this book's discussions: they are typically highly conserved across species; most are highly selective for one ion; they permit extremely rapid ion fluxes; abnormal variants of genes encoding them can cause specific diseases; and their activities can be affected by drugs (Murray and Granner 2006).

The heart's natural electrical activity is discussed in the following chapter. To set the scene for those discussions, it is appropriate here to consider two classes of cardiac ion channels of particular interest, sodium channels and potassium channels. Sodium ion channels are of particular interest with regard to cardiac depolarization (cardiac cells "firing," or contracting), and potassium ion channels are of particular interest with regard to cardiac repolarization (the period in which the cardiac cells are resting and preparing to fire again).

Both channels are members of a large superfamily of ion channels that display characteristics already noted: they are highly selective for one ion, meaning that they favor the translocation of a specific ion from one side of the plasma membrane to the other. The fact that many ion channels are highly conserved across species means that studying ion channels in other species can be highly informative concerning the structure and function of human ion channels.

Sodium ion channels consist of four domains, each of which contains six transmembrane segments. These domains are identical, and the term monomeric is therefore used. The structure of the potassium ion channel of central importance in Chapter 7's discussions, called the hERG channel for reasons explained shortly, differs from sodium ion channels in a relatively subtle but important manner (Turner and Durham 2009). The structure of the hERG channel is tetrameric: four α-subunits, each containing six transmembrane segments, combine to form the channel. The monomeric nature of the sodium channel means that all four domains are always the

same as each other. In contrast, the tetrameric nature of the hERG channel means that the four domains could be the same as each other, i.e., homomeric α-subunits, or they could differ, in which case the channel would be heteromeric. This aspect of the hERG channel's composition gives rise to a greater degree of possible variants.

2.10.1 Focus on the hERG Cardiac Potassium Ion Channel

Repolarization of cardiac myocytes is primarily influenced by the outward flow of potassium ions through potassium channels, i.e., translocation of potassium ions from the intracellular side of the plasma membrane to the extracellular side. Multiple forms of potassium ion channels mediate cardiac repolarization, and each of these is associated with a particular ionic current. One of these ionic currents, I_{Kr}, has been of particular interest in the field of proarrhythmic cardiac safety.

The letter *I* in the field of cardiac electrophysiology derives from the use of this letter in physics to represent a current: the names of multiple ionic currents therefore commence with this letter. The subscript upper case letter "K" (the chemical symbol for potassium) represents that I_{Kr} is a potassium ionic current, and the use of the subscript lower case letter "r" represents that it is the rapid component of the repolarizing I_K current, one of several potassium currents that each flow through one of several potassium channels. Various types of potassium ionic currents are discussed in more detail in Chap. 9: here, we simply focus on I_{Kr} and the ion channel through which it flows.

It has been noted that ion channels can be preserved across species to a remarkable extent. Section 2.6.1 discussed the work of Morgan's group in the field now called transmission genetics that employed *Drosophila melanogaster.* A *Drosophila* gene of great relevance to the field of proarrhythmic safety is called *eag*, which stands for the ether-a-go-go gene. The name originated from the identification of one variant of the gene that was associated with twitching of the fly's legs when anesthetized with ether (part of the normal course of research with them) that some individuals thought bore resemblance those of a (human) go-go dancer. The acronym of the related human gene, hERG, stands for the human ether-a-go-go-related gene. As Turner and Durham (2009) noted, despite a name that some may find flippant, the consequences of abnormal variant hERG genes, and also the consequences of drug-induced alterations in the functioning of ion channels resulting from normal variant hERG genes, are of serious clinical concern and potentially fatal. Given this level of interest in the gene, the acronym hERG is often used in the proarrhythmic literature without provision of its full name in much the same way that the acronym DNA is used in multiple literatures. In this book we have adopted the following approach to nomenclature:

- hERG is the gene that codes for (encodes) the α-subunit of the central pore of one particular cardiac potassium ion channel, referred to as the hERG channel.
- The ionic current that flows through the hERG channel can be referred to as hERG current as well as its formal name of I_{Kr}.

2.10.2 Ion Channel (Protein) Trafficking

Protein trafficking is the process whereby a protein manufactured within a cell is delivered (trafficked) to its desired location within the cell. In the case of hERG channels, it is the process whereby the relevant proteins are delivered to their locations within the plasma membrane.

mRNA translation and protein synthesis occur within the endoplasmic reticulum, a network of interconnected tubules, vesicles, and sacs. To ensure that it folds into the correct three-dimensional tertiary structure, the hERG protein forms a complex with one of several other proteins called cytosolic chaperones. Once folded correctly it is transported in a vesicle to the Golgi apparatus, which consists of various distinct regions, including regions where glycosylation or phosphorylation occurs. Once the fully glycosylated form of the hERG channel protein has been manufactured within the cell, it is packaged into a transport vesicle and taken to the plasma membrane. The three-dimensional orientation of the hERG channel transmembrane protein is maintained so that, once embedded into the plasma membrane, the regions destined to project outside the cell are placed appropriately, as are the regions destined to project inside the cell (Turner and Durham 2009).

Several processes can result in impediments to the natural hERG protein-trafficking process. Two scenarios are of relevance to this book's discussions: correctly formed proteins may not reach the plasma membrane in normal quantities and abnormally formed proteins may reach the plasma membrane and become embedded in it. In both cases, the total degree of hERG current flowing through hERG channels will be less than normal.

2.11 Enzymes

Enzymes are biological polymers and comprise the largest class of proteins. They act as catalysts for almost all of the chemical reactions that occur in living organisms and therefore make life as we know it possible (Kennelly and Rodwell 2006). Catalysts are not consumed or permanently altered as a consequence of their participation in a reaction. Enzymes reduce the activation energy required for each of the stages in reactions by a very considerable amount: they catalyze the conversion of one or more compounds (substrates) into one or more different compounds (products) and thereby enhance the rates of the corresponding non-catalyzed reactions by factors of 10^6 or more.

Catalysis takes place at the enzyme's active site, a specific location on the enzyme macromolecule. The active site is a small component of the enzyme: most of the amino acid residues that comprise the macromolecule do not come into contact with the substrate, serving instead as a backbone that allows the active site to be configured appropriately in three-dimensional space so that it can align with the functional (active) groups of the substrate that it catalyzes. As Weiner (2006, p. 375) noted,

"the distances and angles between the catalytic residues of the enzyme and the substrate must be exact to permit catalysis to occur." This is the reason that enzymes are extremely selective catalysts, selecting for a single substrate (or very small group of them) and the type of reaction catalyzed. The three-dimensional nature of enzymes, and hence of their active sites, facilitates catalysis by shielding the substrates from solvents, i.e., stabilizing them, while they are catalyzed into their respective products (Kennelly and Rodwell 2006).

2.11.1 Metabolic Enzymes

Metabolic enzymatic activity in the liver is one of the body's main neutralization strategies for xenobiotics, including drugs. Drug molecules, the substrates of interest here, are catalyzed into products called metabolites. Drug metabolism can be divided into three phases (Schultz 2006):

- Phase I metabolism. The chemical structure of the compound is modified by oxidation, reduction, or hydrolysis. This process forms an acceptor group.
- Phase II metabolism. A chemical group is attached to the acceptor group. This typically generates metabolites that are more water soluble and are therefore more readily excreted.
- Phase III metabolism. Transporters transport the drug or metabolites out of the cells in which Phase I and Phase II metabolism has occurred.

In Phase I metabolism, the major oxidative drug-metabolizing pathway is catalyzed by cytochrome (CYP) 450 enzymes (Mulder 2006). Genetic differences in drug metabolism between individuals can be largely explained by genetic influences on drug-metabolizing enzymes. The presence of abnormal gene variants can lead to changes in an enzyme's biological activity. If the enzyme becomes less effective or ineffective, the concentration of the drug in the bloodstream will remain higher and could lead to toxic effects (i.e., beneficial effects that become "too" beneficial). Less effective or ineffective enzymatic activity can result in two ways: abnormal variants that result in a needed enzyme not being made, or abnormal variants that result in incorrect manufacture of the enzyme. Another observation of relevance is that gene multiplication may lead to increased expression of a particular enzyme in certain individuals. This leads to the "ultra-rapid metabolizer phenotype."

A telling illustration of the ramification of genetic influence on metabolism is provided by nortriptyline, a tricyclic antidepressant (see Primrose and Twyman 2006). Most patients require 75–100 mg per day (mg/day) to reach a steady-state plasma concentration of 50–150 μg/l. In contrast, poor metabolizers need only 10–20 mg/day, while ultra-rapid metabolizers need 300–500 mg/day to achieve the same plasma concentration. The ultra-rapid metabolism is caused by amplification of the CYP2D6 locus.

The CYP450 group of enzymes mediates most drug functional group metabolic modifications, and hence these enzymes are of considerable importance

when studying drug responses. Of particular importance are CYP1A2, CYP3A, CYP2C9, CYP2C19, CYP2D6, and CYP2E1 (Wijnen et al. 2007). As one example of the degree of genetic variance that can exist, over 70 allelic variants of the CYP2D6 locus have been described: this polymorphism is of considerable relevance since it is implicated in the metabolism of more than 100 drugs (Primrose and Twyman 2006).

2.12 Continued Discussion of Biopharmaceuticals

Having introduced biological considerations and nomenclature in previous sections of this chapter, additional discussion of biopharmaceuticals is now provided.

2.12.1 Recombinant DNA Technology

The very large size of DNA molecules caused considerable problems in the early days of molecular biology. Understanding the precise function of particular stretches of DNA required isolating that part of the DNA molecule and then obtaining enough of it to work with. James Watson, one-half of the Watson and Crick partnership that first proposed the structure of DNA in 1953 (Watson and Crick 1953), commented as follows (Watson 2004, pp. 87–88):

> In essence we needed a molecular editing system: a pair of molecular scissors that could cut the DNA text into manageable sections; a kind of molecular glue pot that would allow us to manipulate those pieces; and finally a molecular duplicating machine to amplify the pieces that we had cut out and isolated.

In 1973 many earlier discoveries came together in the form of recombinant DNA technology, "the capacity to edit DNA" (Watson 2004). Enzymes can be used to create fragments of DNA and to join different fragments together. Restriction enzymes can cut DNA molecules internally at defined positions, creating predictable fragments with specific base pair sequences. Other enzymes called DNA ligases can join DNA fragments together. The novel arrangements created in this manner are called recombinant DNA molecules. Some of them have become biopharmaceutical drugs (biotechnology is not exclusively related to making drugs). Walsh (2003) addressed the beginning of the modern biotechnology era as follows:

> Advances in our understanding of the molecular principles underlying both health and disease has revealed the existence of many regulator polypeptides of significant medical potential. The fact that such polypeptides are produced naturally within the body only in minute quantities initially precluded their large-scale medical application. The development in the 1970s of the twin techniques of genetic engineering and hybridoma technology marked the birth of the modern biotech era. These techniques facilitate the large-scale production of virtually any protein, and proteins of medical interest produced by these methodologies have been coined 'biopharmaceuticals.'

While the term biopharmaceutical has been defined in various ways in the literature, the definition provided by Walsh (2003) is useful for our purposes: "The term biopharmaceutical refers to protein or nuclei acid based pharmaceutical substances used for therapeutic or in vivo diagnostic purposes, which are produced by means other than direct extraction from natural (non-engineered) biological sources." Most biopharmaceuticals have been discovered as a direct consequence of increased knowledge and understanding of the body's molecular mechanisms that underpin states of health and disease.

Genetic engineering has facilitated the availability of pharmaceutically important proteins in several ways. Most proteins that have therapeutic potential are produced naturally in the body in only minute quantities. Examples include interferons, interleukins, and colony-stimulating factors. This means that the proteins' direct extraction from naturally available sources in quantities sufficient to meet likely clinical demand is problematic. Genetic engineering facilitates the manufacture of as much of a protein as is needed.

Additionally, while nature has optimized protein structures for their natural biological activities (some of which were described earlier in this chapter), these natural structures may not be optimal for medicinal applications. Recombinant DNA technology, perhaps more often called genetic engineering, is therefore employed to reengineer the protein structure to enhance relevant characteristics (Levine 2006). The technique of site-directed mutagenesis facilitates the deliberate engineering of predefined changes in a protein's amino acid sequence. Such changes can be minimal such as the insertion, deletion, or alteration of a single amino acid residue or can be more substantial. These changes can be made for a variety of reasons, and several engineered products have gained marketing approval, including both faster-acting and longer-acting insulins.

2.12.2 A Case Study: Genetically Engineered Insulin

Human insulin, a hormone, plays a central role in regulating blood glucose levels within normal limits throughout the day by lowering blood glucose levels via inhibition of the production of glucose in the liver. Endogenous insulin is formed in a multistep process. Preproinsulin is synthesized in the endoplasmic reticulum of beta cells in the pancreas. It is rapidly converted to proinsulin, which consists of the A chain, the B chain, and a 35-amino-acid intervening connecting segment known as "C-peptide." Conversion of proinsulin to insulin occurs in the Golgi apparatus when the C-peptide is cleaved out, and the A and B chains are joined by disulfide bonds. Because exogenous insulin and insulin analogues do not contain C-peptide, the presence of C-peptide in a blood test allows an assessment of endogenous insulin secretion, even in the presence of exogenous insulin or insulin analogues.

Chain A has 21 amino acid residues and chain B has 30 residues. Recombinant DNA technology provides the ability to manufacture recombinant insulin or insulin analogues. Insulin lispro is identical to human insulin except for amino acid

insertions at locations B29 and B30. Insulin aspart differs from human insulin at just one location, B28, where the amino acid aspartic acid is substituted for proline: the name insulin aspart reflects the substitution of aspartic acid. Insulin aspart provides an interesting example of how a small change in a protein's structure can have a significant impact on its function. The single amino acid substitution compared with endogenous insulin reduces the aggregation of insulin molecules, which means that this form of insulin dissociates rapidly and is therefore absorbed rapidly (Brenner and Stevens 2006).

Specific guidance for insulin analogues is provided by FDA and EMA. The FDA's February 2008 draft guidance document on the development of diabetes drugs (FDA 2008) commented that in the development of a new insulin analogue, sponsors should address the following three fundamental issues in randomized, controlled trials:

- The risk of hypoglycemia. This should be addressed under the conditions of use ultimately recommended in labeling, relative to approved insulin products and regimens.
- Pharmacokinetic variability. This should be evaluated according to injection site, thickness of fat layer, and other parameters known to affect absorption, distribution, metabolism, and excretion characteristics. Additionally, pharmacodynamic characteristics should be carefully studied to direct dosing interval (for long-acting products) and timing of dosing relative to meals (for short-acting products).
- Immunogenicity. As a complex biological protein, insulin has the potential to be immunogenic. Adequate assays should therefore be developed that measure antibodies to the test product before the submission of an application.

The EMA's latest thinking (as of writing this chapter) on this topic is captured in their March 2015 document (EMA 2012) providing an overview of comments received following the release of their draft revised "Guideline on nonclinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues" in December 2012 (EMA 2015).

2.13 Manufacturing Considerations

Once a drug has received marketing approval, successful commercialization of the approved drug has its own demands. These include the sponsor's ability to manufacture sufficient quantities of the drug in a form that can be readily transported from the manufacturing plant to the pharmacy from which it will be dispensed and in a form that also demonstrates the necessary stability to enable a suitably long shelf life.

The manufacture of both pharmaceutical and biopharmaceutical drugs differs according to the stage of development. Initially, very small amounts of the drug are needed, and this "manufacturing" typically occurs on a laboratory scale. The amount

of drug candidate needed becomes progressively larger as the clinical development program proceeds. Eventually, once the drug is approved by a regulatory agency, commercial-scale manufacturing is needed. The transition from small-scale production to commercial-scale manufacturing is far more complex than simply building proportionately larger manufacturing equipment, especially in the biopharmaceutical domain: manufacturing processes cannot easily be scaled or proportionally increased to produce commercially useful quantities of the drug, and different instruments and analytical techniques are needed (Ho and Gibaldi 2003). While our primary focus is on the cardiovascular safety of drugs during development and therapeutic use, it is informative to consider manufacturing processes briefly: this is an often neglected topic in books that are not exclusively devoted to it, and the challenges are therefore often not appreciated by those not directly involved in the processes. Discussions here focus on commercial-scale manufacturing.

As Monkhouse (2006, p. 2) observed, "The difficulty of converting a laboratory concept into a consistent and well-characterized medical product that can be mass-produced has been highly under-rated." As just one example, consider stability testing. Tsong and colleagues (2006) defined the stability of a drug product as its capacity "to remain within the established acceptance criteria to ensure its identity, strength, quality, and purity within a specified period of time." Stability testing permits the determination of the length of time that the drug product is expected to remain within the approved acceptance criteria as long as the drug product has been stored as stated on the container label. At the manufacturing facility, an expiration date is placed on the package containing the drug, stating the date after which the drug should not be used. In this manner, the shelf life of the drug is communicated. The reason this information is important is that, once manufactured, drug products are exposed to many environmental conditions, e.g., light, temperature, and humidity, which can lead to their chemical decomposition (Florence and Attwood 2006). It is therefore important to know how well the drug product withstands these environmental assaults.

2.13.1 Manufacturing Recombinant Protein Biopharmaceuticals

Most small-molecule drugs are produced by direct chemical synthesis. Multiple steps can be involved as various intermediate molecules are created on the pathway to eventually synthesizing the desired molecule. In contrast, larger-scale manufacture of biopharmaceuticals involves the employment of host cells to produce proteins that are safe and effective (Ho and Gibaldi 2003). The choice to use prokaryote host cells (prokaryotes are microorganisms with no distinct membrane-bound nucleus), lower eukaryote cells, or higher eukaryote (mammalian) cells, which becomes progressively more expensive in the order just listed, is predicated on what kind of host cell is needed to carry out necessary posttranslational modifications,

including glycosylation, and hence best express the recombinant protein of interest.

Production of protein biopharmaceuticals synthesized in prokaryotic or eukaryotic cells can be divided into three stages (Walsh 2003):

- Upstream processing: The fermentation process that initially generates the product.
- Downstream processing: Purification of the protein product and placing the product into the finished format. This includes filling the product into its containers and sealing the containers.
- Labeling and packaging.

Downstream processing involves employment of a purifying system that can isolate the product in as few steps as possible using the simplest purification technology that will achieve the required purity. While purity is a critical consideration for both small-molecule pharmaceuticals and biopharmaceuticals, the nature of biopharmaceutical administration (typically, at least to date, via injection) and the nature of biotechnology processes used in their manufacture require that additional considerations be paid to their purity. The final product must meet regulatory purity and sterility standards and must be below the maximally acceptable cellular or microbial contamination levels (Ho and Gibaldi 2003).

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Chapter 3

Cardiovascular Structure, Function, and Pathophysiology

The heart is a supreme example of biomechanical engineering that, under normal circumstances, operates with elegant economy (Turner 1994).

3.1 Introduction

This chapter provides an overview of healthy cardiovascular structure and function, followed by an overview of cardiac pathophysiology and disease. In each case, attention falls first on the heart, since multiple subsequent chapters focus on proarrhythmia. Nonetheless, discussions of the cardiovascular system are also pertinent to topics addressed later in the book.

The heart is a supreme example of biomechanical engineering, and, under normal circumstances, it operates with elegant economy (Turner 1994). As acute metabolic demand varies with increases and decreases in skeletal muscular activity, cardiac activity adapts commensurately, enabling skeletal musculature to receive appropriate supplies of blood, and hence oxygen, to facilitate its physical activity. This intimate and biologically sensible arrangement is complemented by blood flow within the systemic vasculature, which (under normal circumstances) ensures adequate oxygen supply to all bodily tissues.

3.2 The Heart

The human heart is a dual muscular pump: both the left side and the right side have an upper chamber, or atrium, and a lower chamber, or ventricle. Blood flowing through the cardiovascular system distributes oxygen (and other nutrients) to cells and also collects carbon dioxide. Deoxygenated blood containing carbon dioxide returns to the right atrium and is sent via the right ventricle to the lungs. Carbon dioxide is removed from the blood, which is also reoxygenated. The oxygen-rich blood flows to the left atrium, from which it passes into the left ventricle, which ejects it into the aorta. Blood is then distributed through the body via arteries,

J.R. Turner et al., *Cardiovascular Safety in Drug Development and Therapeutic Use*, DOI 10.1007/978-3-319-40347-2_3

arterioles, and body tissue capillaries, where exchange of oxygen and carbon dioxide occurs. Blood then flows back to the heart via capillaries, venules, and veins.

The heart muscle, or myocardium, surrounds both sides of the heart and influences the flow of blood through all four heart chambers by its regular pattern of squeezing and then relaxing. Valves within the heart control the flow of blood in the desired directions (each atrium to the respective ventricle and from each ventricular into the respective artery). The locations of heart valves are as follows:

- The tricuspid valve is between the right atrium and right ventricle.
- The pulmonary valve is between the right ventricle and the pulmonary artery.
- The mitral valve is between the left atrium and left ventricle.
- The aortic valve is between the left ventricle and the aorta.

A specialized network of blood vessels called the coronary circulation supplies the heart. Coronary arteries branch off the aortic root just distal to the attachments of the aortic valve leaflets and are therefore the first arteries to branch off the aorta. The right coronary artery supplies oxygen to the right side and usually the bottom of the heart. The left coronary artery divides into two branches, the anterior descending branch and the circumflex branch. The anterior descending branch supplies blood to the left side of the heart and the interventricular septum, and both the anterior descending branch and the circumflex branch supply blood to the lateral aspect and rear of the heart. By curling around the heart and dividing into smaller and smaller branches, the coronary arteries are able to supply every muscle fiber in the myocardium with blood and, hence, oxygen (Turner and Durham 2009).

3.2.1 The Cardiac Cycle and the Action Potential

The discipline of cardiac electrophysiology studies how the cardiac conduction system facilitates the flow of electrical stimuli across cardiac tissues. The discipline is employed in clinical practice for the diagnosis of cardiac rhythm abnormalities and pathophysiology and can also be used in proarrhythmic cardiac safety evaluations: our attention will focus on the latter.

The electrocardiogram (ECG) is a well-known pattern of electrical activity. For present purposes, a simplified approach can be adopted, with focus falling on just one of the multiple intervals that can be identified on an ECG. Figure 3.1 is a stylistic representation of an ECG waveform, with the landmarks and interval of interest identified. These are the onset of the QRS complex, the offset of the T-wave, and the distance between these two points, known as the QT interval. Given that drug-induced prolongation of the QT interval is of considerable importance in the book's discussions, a stylistic representation of QT interval prolongation is shown in Fig. 3.2.

It should be noted that the landmarks defining the QT interval were deliberately made very clear in Figs. 3.1 and 3.2. In actual cases, the precise identification of these landmarks, particularly the offset of the T-wave, can be extremely difficult to

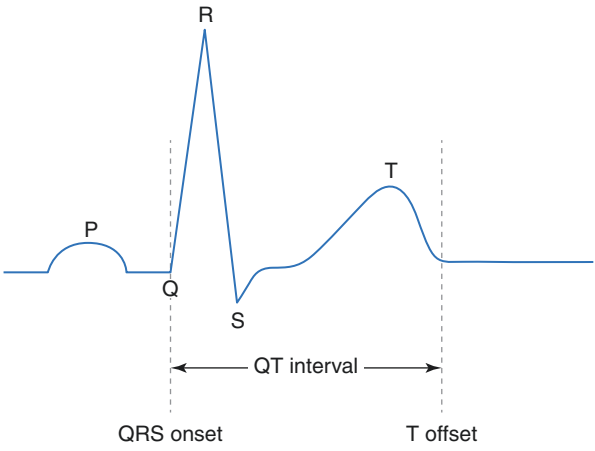

Fig. 3.1 Stylistic representation of the ECG waveform

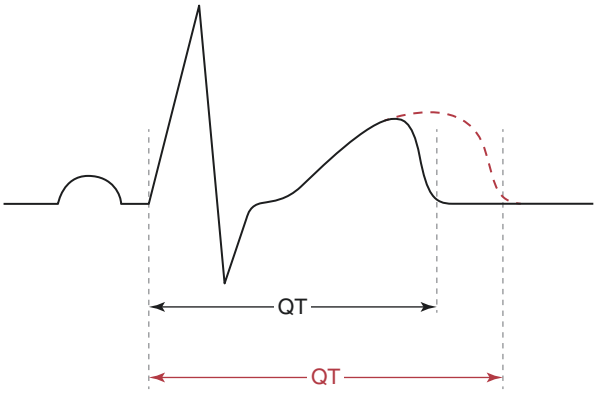

Fig. 3.2 Stylistic representation of QT interval prolongation

identify, and strategies to optimize the accuracy of identification are discussed in Chap. 7 in the context of proarrhythmic cardiac safety research.

Cardiac cells are surrounded by a membrane, and the cell's intracellular environment has a negative electrical charge compared with the cell's immediate extracellular environment. The voltage difference across the cell membrane is termed the transmembrane potential. In between cardiac contractions, the resting transmembrane potential is around minus 80 millivolts (−80 mV) to −90 mV. The greater negativity inside the cell results from an accumulation of relatively more negatively charged ions than positively charged ions inside the cell. Intrinsic electrical stimulation from the heart's natural pacemaker causes a cascade of ion channels in the cell's membrane to open and close rapidly. In simple terms, depolarization (which means the transmembrane potential moving back towards zero) is achieved by an influx of positively charged sodium ions through sodium ion channels. This is associated with the initiation of the cardiac contraction or heartbeat. Repolarization (the potential moving back towards −80 mV) is achieved by the efflux of positively

charged potassium ions: less positive charges within the cell means that the transmembrane potential moves towards a more (negatively) polarized level again. In more accurate terms, the change in transmembrane potential from the resting level at each point in time across the cardiac cycle is the net result of incoming and outgoing ions moving through multiple sodium and potassium ion channels (and also calcium channels and ion pumps, which for simplicity are not discussed in this chapter) resulting in local changes in net electrical charge on either side of the cell membrane. These resulting voltage fluctuations can be graphed against time to yield the cell's action potential.

A stylistic representation of the action potential, represented as phase 0 through phase 4, and ionic currents influencing the action potential at each phase can be seen as Fig. 1a in an Open Access paper by Sager and colleagues (2014), and a detailed description of the ionic currents of particular relevance to related discussions in Chap. 9 is presented in Table 9.1. The voltage spike resulting from a given cell's depolarization tends to cause adjacent cardiac cells to depolarize by causing their sodium channels to open. Once a cardiac cell is stimulated to depolarize, an electrical impulse is propagated across the heart, cell by cell, by a wave of depolarization. The speed of a cell's depolarization is reflected by the slope of phase 0 of the action potential: the steeper the slope (i.e., the closer it is to vertical), the faster the rate of depolarization.

Once a cardiac cell has been depolarized, it cannot be depolarized again until repolarization has occurred. At normal resting heart rates (around 75 beats per minute for adult males, and somewhat higher for adult females), there is less than one second for both depolarization and repolarization to occur: this timespan decreases considerably at heart rates that are achieved during vigorous exercise. Therefore, repolarization must happen (very) quickly. The time taken by the process of repolarization is called the refractory period. Its length corresponds roughly to the time for phases 1 through 3 of the action potential to occur.

3.3 Cardiovascular System Parameters of Interest

Four cardiovascular parameters of interest are stroke volume, cardiac output (CO), total peripheral resistance of the systemic vasculature (TPR), and blood pressure. Measurements of both systolic blood pressure (SBP) and diastolic blood pressure (DBP) are typically presented when discussing blood pressure.

3.3.1 Stroke Volume and Cardiac Output

Stroke volume is the amount of blood pumped into the aorta per heartbeat. It is typically measured in milliliters (ml), and a typical stroke volume is around 60–100 ml. Cardiac output is the total amount of blood pumped per unit of time, typically 1 min. As is the case for heart rate, CO is usually represented in intervals of 1 min and is

measured in liters per minute (lpm). A typical CO for an adult resting quietly is about 5–6 lpm. This can increase several fold as needed during physical activity: it can also increase during emotional stress.

3.3.2 Total Peripheral Resistance of the Systemic Vasculature

Along with CO, TPR is the second primary determinant of blood pressure. The simultaneous measurement of blood pressure and CO allow the derivation of TPR. It is the resistance provided by the vasculature to the ejection of blood into the aorta. Blood pressure can be thought of as representing a manifestation of the interaction between the heart and the vasculature (Obrist 1981). A given change in blood pressure can be the result of a change in cardiac output, a change in TPR, or a combination of both.

3.3.3 Blood Pressure

There is continuous pressure in arteries to propel blood through them. The level of blood pressure fluctuates during each cardiac cycle. Pressure is highest during systole (contraction) when blood is ejected from the left ventricle into the aorta: this pressure is labeled SBP. Pressure is lowest during diastole (relaxation) and labeled DBP.

The unit of blood pressure measurement received its name, millimeters of mercury (mmHg), during a period of time in which a catheter was placed into the brachial artery in the arm, and blood was channeled to the bottom of a tube of mercury. The height of the mercury column varied during the cardiac cycle due to the fluctuations in blood pressure: the pressure at each point in time caused the column of mercury to rise to a certain height. This height was measured in millimeters, and hence the unit mmHg. Modern measurement techniques are noninvasive in nature and no longer require the use of mercury.

Given the importance of blood pressure measurement to diagnose high blood pressure, or hypertension (see Sect. 3.4.4), a methodological incongruity should be highlighted here: while it is remarkably (and arguably scarily) easy to obtain ***a*** blood pressure reading, it can be disturbingly difficult to estimate the ***correct*** blood pressure reading in a given circumstance (Turner 2010). Going one step further, it is not as straightforward as one might imagine to operationally define "correct" in this context. Pickering and colleagues provided useful insights, observing that "Any clinical measurement of blood pressure may be regarded as a surrogate measure for the 'true' blood pressure of the patient, which may be defined as the mean level over prolonged periods" (Pickering et al. 2006). In general medical practice, it is common for a single blood pressure to be taken by a physician or other health-care professional. Two questions therefore arise: Is the reading taken an accurate representation of blood pressure at that moment? And, even if it is an accurate

measurement, is it a meaningful representation of the patient's "true" blood pressure, defined, as just noted, as the mean level over prolonged periods of time?

An alternate blood pressure measurement modality involves multiple readings being taken by a fully automated device while the patient rests quietly and alone in a room within the physician's office suite. Advantages include improved accuracy, reduced digit preferences (e.g., the tendency of a human reader to "round up" or "round down" values to the nearest value ending in a zero or a five), the reduction of the influence behind white-coat hypertension (discussed momentarily), and a stronger relationship between readings taken in this manner with target organ damage compared with manual readings (Andreadis et al. 2011). Myers and colleagues have advocated for automated office blood pressure measurement to replace traditional office blood pressure assessment (Myers 2010, 2014; Myers and Godwin 2012).

In the last two decades, a considerable literature discussing home blood pressure monitoring has accumulated (see Stergiou et al. 2014). Stergiou and colleagues have discussed advantages of home blood pressure monitoring, including the following: prediction of preclinical target organ damage and cardiovascular events in a manner superior to clinic blood pressure measurements and improvement of long-term adherence to antihypertensive drug treatment in treated hypertensive patients and hence improved hypertension control rates. The authors commented that, as long as current recommendations are followed, home blood pressure monitoring should have a "primary role in diagnosis, treatment adjustment, and long-term follow-up" of most cases of hypertension (Stergiou et al. 2014). It should be noted, however, that home blood pressure gives no indication of blood pressure during sleep (O'Brien et al. 2013).

Ambulatory blood pressure monitoring, widely considered to be the "gold standard" for evaluating true levels of blood pressure over a prolonged period of time, facilitates collection of blood pressure readings several times an hour across a 24-h period (Turner et al. 2015). These readings can be aggregated to yield 24-h means and also grouped into time windows, e.g., mean daytime and nighttime values (Pickering et al. 2006; O'Brien 2012). These various blood pressure categorizations are valuable for clinical management of high blood pressure because they increase the accuracy for diagnosis and the prediction of cardiovascular risk (Krakoff 2013). Ambulatory blood pressure monitoring enables white-coat hypertension to be ruled out, thus precluding patients who do not need pharmacologic interventions at that time from being prescribed such intervention, while also identifying those individuals who should commence antihypertensive therapy. It also facilitates the assessment of BP during sleep time: a non-dipping pattern and nocturnal hypertension are strongly associated with increased cardiovascular morbidity and mortality (Turner et al. 2015).

3.4 Cardiac and Cardiovascular Diseases and Occurrences of Clinical Concern

While there are multiple cardiac and cardiovascular diseases, this section presents brief reviews of a relatively small subset that are of relevance to discussions later in the book.

3.4.1 Arrhythmias

Arrhythmias, abnormal cardiac rhythms, are disorders of cardiac impulse generation and propagation. Both atrial and ventricular arrhythmias can occur. The term bradycardias refers to slower than usual patterns of cardiac contractions: tachycardias are faster than usual patterns.

Atrial arrhythmias include atrial flutter and atrial fibrillation. During atrial flutter, the atria contract in a regular but very rapid pattern. During atrial fibrillation (AFib), the number of beats per minute is even higher, and, of importance, the pattern is irregular. At least 30 million people worldwide carry a diagnosis of AFib, and many more likely have undiagnosed, subclinical, or "silent" AFib. Atrial fibrillation-related cardiovascular morbidity and mortality includes heart failure, stroke, hospitalizations, and cardiovascular deaths (Kirchhof et al. 2016).

Ventricular arrhythmias include premature ventricular contractions, ventricular tachycardia, and ventricular fibrillation. Premature ventricular contractions occur when the ventricles occasionally contract earlier than usual, and the electrical origin of the beat is within the ventricle and not the atria or the atrioventricular node. This can often be felt as a "skipped" heartbeat, a common condition that is typically not of clinical concern. However, two or more of these occurring together can be a warning sign of more serious arrhythmias. Ventricular tachycardia can be caused by irritated myocardial cells, for which there are multiple reasons. These cells cause a regular but rapid heart rate that often leads to inefficient pumping. Ventricular tachycardia can deteriorate to ventricular fibrillation, the major underlying cause of sudden cardiac death (Boukens et al. 2015). This occurs when myocardial cells contract in a totally disorganized fashion, resulting in the heart no longer pumping blood around the body.

3.4.2 Torsades de Pointes

Torsades de pointes (*torsades*) (Dessertenne 1966; Fabiato and Coumel 1991) is a particular form of ventricular tachycardia that has three defining characteristics on an ECG recording:

- It is associated with QT interval prolongation.
- The shape of the QRS complex (QRS morphology) twists around an imaginary axis.
- The QRS complex takes on many morphologies as it twists around this imaginary axis, leading to the descriptor polymorphic.

The first characteristic listed indicates that the term *torsades* is reserved for polymorphic ventricular tachycardia associated with QT interval prolongation: in the absence of QT prolongation, the descriptor should simply be polymorphic ventricular tachycardia.

3.4.3 *Cardiac Channelopathies I: Long QT Syndrome*

Inherited ion channel pathophysiologies are referred to as channelopathies. Some cardiac channelopathies lead to inherited long QT syndrome (LQTS) (see Nakano and Shimizu 2016). Bunch and Ackerman (2007) observed that the discipline of cardiac channelopathies began in 1995 with the discovery of mutations in genes encoding critical cardiac ion channels. Schwartz (2005, p.186) commented on this occurrence as follows:

The identification at the end of March 1995 (Wang et al. 1995; Curran et al. 1995) of the first two long QT syndrome (LQTS) genes represented a major breakthrough not only for cardiac electrophysiology but also for cardiology as a whole and paved the way for the understanding of how tight the relationship between molecular and clinical cardiology can be. Indeed, the impressive correlation between specific mutations and critical alterations in the ionic control of ventricular repolarization has made LQTS the best example to date for the specificity and value of the correlation between genotype and phenotype.

There are multiple LQTSs, each of which is the result of a specific genetic mutation. Given our primary focus on potassium and sodium cardiac ion channels (calcium channels are addressed in Chap. 9), Table 3.1 presents three LQTSs as examples: LQT1, LQT2, and LQT3. In each case, the gene in which the mutation occurs, the ionic current that is affected, and the consequence of the genetic mutation are listed. These mutations involve either loss-of-function potassium ion channel mutations (less current flows through the channel) or gain-of-function sodium ion channel mutations (more current flows through the channel, or current flows for a longer period of time).

LQTS may be detected via the identification of QT prolongation on an individual's ECG before any clinical manifestations present themselves. However, given the complexities of identifying QT prolongation in many cases, a topic discussed in detail in Chap. 7, such detection does not always happen. Clinical manifestations of LQTS can be dramatic and very dangerous: it can present as abrupt-onset syncope

Table 3.1 Long QT syndromes LQT1, LQT2, and LQT3

Channelopathy	Gene in which mutation occurs	Ionic current affected	Consequence of mutation
LQT1	KCNQ1	I_{Ks}	Decrease in the repolarizing I_{Ks} potassium current: net repolarizing influence is lessened
LQT2	KCNH2	I_{Kr}	Decrease in the repolarizing I_{Kr} potassium current during repolarization: net repolarizing influence is lessened
LQT3	SCN5A	I_{Na}	Gain of function in (or persistence of) the I_{Na} sodium current, a depolarizing influence: net repolarizing influence is lessened

Modified from Turner and Durham (2009)

(loss of consciousness), seizures, or sudden cardiac death due to *torsades*. Some sudden deaths having origins in a channelopathy may have been presaged by unrecognized warning signs including syncope brought on by physical exertion or by a positive family history of premature sudden death where causes were not identified.

Detailed discussions of drug-induced QT interval prolongation later in the book make LQT2 of particular relevance here. As seen in Table 3.1, this LQTS results from a decrease in I_{Kr}. For reasons of molecular biology and the interaction of small-molecule drugs with biological structures, it happens to be the case that drug-induced QT prolongation is commonly produced as the result of drug molecules being trapped inside the cardiac channel through which I_{Kr} flows: in other words, it is the result of a decrease in I_{Kr}. Given that LQT2 is of considerable concern and that drug-induced QT prolongation is commonly the result of a decrease in the same ionic current as is seen in LQT2, drug-induced QT prolongation also becomes of clinical concern.

It is worth noting here that while discussion in subsequent chapters rightly focuses on the unwanted consequences of drug-induced QT prolongation, the identification of nonlethal drug-induced QT prolongation in an individual can sometimes be the sentinel event leading to the serendipitous identification of the inherited disorder LQTS: the individual may then benefit from clinical intervention (Turner and Durham 2009).

Section 3.5 reviews a different set of channelopathies comprising cases of short QT syndrome (SQTS). While these channelopathies and their drug-induced phenotypic counterparts are not of central importance in this book's discussions, they are certainly worthy of inclusion in this chapter.

3.4.4 Hypertension

High blood pressure is currently the greatest threat to the global burden of disease (Horton 2013; Das and Samarasekera 2013; Lim et al. 2013): it continues to be the most common diagnosis in adult primary care practice and the most salient risk factor for cardiovascular disease (Turner et al. 2015). Hypertension is the most common cardiovascular disease in the USA and many other industrialized countries: for example, approximately 80 million adults in the USA have been diagnosed with high blood pressure (American Heart Association web site). Two characteristics make hypertension particularly dangerous. First, it has no direct symptoms: an individual can have high blood pressure for years without being aware of this condition (hypertension is often discovered while visiting the doctor for another complaint). Second, it contributes strongly to the etiology of several other cardiovascular diseases. Taken in conjunction, these characteristics mean that considerable arterial and organ damage can occur during the time that hypertension remains undetected.

The American Heart Association's (AHA's) web site presents several blood pressure categories, shown in Table 3.2:

Table 3.2 Blood pressure categories defined by the AHA

Category	SBP (mmHg)		DBP (mmHg)
Normal	<120	And	<80
Prehypertension	120–139	Or	80–89
Stage 1 hypertension	140–159	Or	90–99
Stage 2 hypertension	160 or higher	Or	100 or higher
Hypertensive crisis (emergency care is needed)	>180	Or	>110

Modified from the AHA's web site

3.4.5 Myocardial Infarction

Approximately 500,000 episodes of acute myocardial infarction occur each year in the USA (Wang et al. 2015). The area of myocardium damaged by a heart attack depends on which coronary artery was blocked, preventing blood and hence oxygen from reaching that area.

The precise definition of a myocardial infarction is a subject of detailed discussion in the literature. Different definitions can be used in clinical practice, clinical trials, and registries (White et al. 2014). In an attempt to standardize definitions, the Third Universal Definition of myocardial infarction is based on troponin elevation together with ischemic symptoms, ischemic ECG changes, and imaging evidence: myocardial infarctions are classified into several types according to whether they are spontaneous, secondary to imbalance between coronary artery blood supply and demand, related to sudden death, or related to revascularization procedures (White et al. 2014).

The typical pain from a heart attack may feel like angina at first but usually becomes more widespread and more severe and lasts longer. Heart attack victims often experience weakness, sweating, and a fear of dying in addition to their chest pain. However, if only a small area of myocardium is injured, it may cause relatively little chest pain that may be mistaken for heartburn. Some patients can have a small heart attack without experiencing any pain. Patients who survive a heart attack are at risk for developing several complications, including arrhythmias and heart failure.

3.4.6 Heart Failure

The term heart failure should not be taken in the literal sense that the heart has failed and is not pumping any blood and death therefore ensues in a matter of minutes if no action is taken. Rather, heart failure refers to a condition where the heart is pumping in a less-than-optimal manner (AHA web site). The heart is therefore providing a less-than-optimal oxygen supply, resulting in shortness of breath and fatigue during everyday activities.

Heart failure is a major public health concern (Gedela et al. 2015). It has been recently categorized into heart failure with reduced and preserved ejection fraction: mortality remains similarly high for both conditions.

The heart can implement various compensatory strategies. The chambers of the heart can enlarge (dilatation), or the heart muscle can thicken (hypertrophy) depending on the etiology of the problem. Usually both will occur which allows the heart to maintain cardiac output, at least at first. If hypertrophy alone occurs, generally the amount of blood pumped with each beat will be reduced. The undesirable consequences of heart enlargement include bodily fluid retention affecting the lungs (the term congestive heart failure is sometimes seen) and arrhythmias. As the condition progresses, the body will divert blood away from certain tissues it considers less essential, such as the kidneys and skeletal muscle, to preserve flow to the brain.

For reviews of the epidemiology of heart failure in Europe and Asia, respectively, see Maggioni (2015) and Sato (2015).

3.5 Cardiac Channelopathies II: Short QT Syndrome

As Antzelevitch and Francis (2004) noted, inherited LQTS was first described in individuals with structurally normal hearts six decades ago by Jervell and Lange-Nielsen (1957). In contrast, inherited SQTS was first proposed as a new inherited clinical syndrome less than two decades ago by Gussak and colleagues (2000). Included in their clinical report was a description of three members of one family: a 17-year-old female, her 21-year-old brother, and their 51-year-old mother. The sister's QT interval was 280 msec at a heart rate of 69, the brother's QT interval was 272 msec at a heart rate of 58, and the mother's QT interval was 260 msec at a heart rate of 74. The shorter than usual QT interval was associated in the sister with several episodes of paroxysmal atrial fibrillation requiring electrical cardioversion. Similar ECG changes seen in a 37-year-old individual not related to the family were associated with sudden cardiac death (Gussak et al. 2000).

Another report of interest was provided by Gaita and colleagues (2003). Several members of two different families were referred for syncope, palpitations, and resuscitated cardiac arrest in the presence of a positive family history for sudden cardiac death. All individuals displayed no evidence of structural heart disease and had a constantly and uniformly short QT interval: at baseline, they all exhibited a QT interval ≤ 280 ms and QTc ≤ 300 ms. The authors concluded as follows (Gaita et al. 2003):

The short QT syndrome is characterized by familial sudden death, short refractory periods, and inducible ventricular fibrillation. It is important to recognize this ECG pattern because it is related to a high risk of sudden death in young, otherwise healthy subjects.

A year later, Brugada and colleagues (2004) reported their study of three families with SQTS and a high incidence of ventricular arrhythmias and sudden cardiac death. In two families, a mutation was identified in the hERG gene. As shown in Table 3.1, this is the gene that encodes the hERG channel through which I_{Kr} flows. The mutation in that case, which led to a decrease in the repolarizing I_{Kr} and hence a decreased net repolarizing influence, led to LQT2. In this case, a different mutation

led to an *increase* in I_{Kr}, an increase in net repolarizing influence, and hence a shortened QT interval. As for LQTS, there are multiple forms of SQTS. The form just discussed, a gain of function in the hERG channel and associated QT shortening, is called SQT1.

3.5.1 Origins of Regulatory Interest in Drug-Induced QT Interval Shortening

As discussed in detail in Chap. 7, realization that some drugs could lead to the same phenotype as LQTS (a prolonged QT interval), led to scientific, clinical, and regulatory interest in this phenomenon in the late 1990s. This in turn led to the release in 2005 of two guidelines from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), which have subsequently been adopted by regulatory agencies. ICH S7B focused on nonclinical examination of drug-induced decreases in I_{Kr}. ICH E14 focused on preapproval clinical assessments of drug-induced prolongation.

With the increased awareness of SQTS and its association with adverse cardiac events in the early 2000s, interest began to focus also on drug-induced QT shortening. Kang and colleagues (2005) reported nonclinical studies demonstrating that the drug compound RPR260243 shortened the QT interval, commenting that "We believe RPR260243 represents the first known hERG channel activator" (Kang et al. 2005). Zhou and colleagues (2005) described several other QT-shortening drugs. Shortly thereafter, Shah (2007) commented as follows:

> As new compounds that shorten the QT interval progress further into clinical development and reach regulatory authorities for approval, questions will inevitably arise on the significance of drug-induced shortening. Therefore, it is not surprising that drug-induced shortening of the QT interval is emerging as another issue of potential clinical and regulatory concern.

3.5.2 Current Thinking on This Issue

As of writing this chapter, a regulatory landscape for the formal assessment of drug-induced QT shortening has not occurred. A paper e-published in March 2016 by Malik addresses this issue in detail (Malik 2016). Readers are encouraged to read his paper once you have read Chaps. 7 and 9, since those chapters provide background material (including nomenclature) to enable the greatest insights from his work. Here, we will simply note his conclusions:

- At present, there is little proof of QT-shortening drugs causing ventricular fibrillation in more than rare isolated instances.
- Comparisons of the incidence of the congenital syndromes show that short QT syndrome is much rarer than long QT syndrome, similar to the findings of short QT intervals compared with long QT intervals in the general population.

- Population exposure to drug-induced QT shortening is likely substantially lower compared with QT prolongation.
- The most frequent sources of cardiovascular stress and of consequently reduced repolarization reserve (e.g., heart failure, liver failure, and kidney disease) all prolong the QT interval.
- Since novel QT-shortening drugs have been shown to minimize or eliminate early after-depolarizations, beneficial antiarrhythmic effects in heart failure patients are possibly more likely.
- Purely theoretical concepts of pharmaceutical risk cannot be used to develop regulatory guidance.
- While novel drugs with marked QT-shortening effects will eventually be developed and reach clinical trials, ECG investigations guided by regulatory guidance focusing specifically on drug-induced QT prolongation will pick up marked QT shortening.
- While it is true that there are some individuals at substantial risk if exposed to QT-shortening drugs, they are in such a minority that, from a public health perspective, focusing on their identification rather than on the restriction of QT-shortening drugs is appropriate.
- At present, no additional tests and/or general acceptance restrictions are needed for the approval of QT-shortening drugs.

Drug-induced QT shortening is therefore not addressed further in this book.

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Part III
A Primer of Statistical Considerations

Chapter 4

Analyzing and Reporting Efficacy Data

Our interest in the discipline of Statistics is a pragmatic one since it provides the best way currently available to conduct clinical development programs (Turner 2010).

4.1 Introduction

When faced with the myriad challenges in drug development, the discipline of Statistics (recognized by the use of an upper case "S") is "the knight in shining armor" that rides to our assistance and facilitates the collection, analysis, and interpretation of optimal-quality data as the basis for rational decision-making at all stages of the process (Durham and Turner 2008). In this and the following two chapters, we have resisted the temptation to provide exhaustive discussion of subtle nuances of statistical analysis: our interest in the discipline of Statistics is a pragmatic one since it provides the best way currently available to conduct clinical development programs.

We noted in Chap. 1 that, since no biologically active drug is free from the possibility of causing adverse reactions in certain individuals who are genetically and/or environmentally susceptible, regulators have to balance a drug's therapeutic benefit with its toxicity to assess the drug's benefit–risk balance. Therefore, it is important to have a fundamental understanding of assessments of benefit, which is called efficacy in clinical trials. Quantitative information concerning both efficacy and safety provides the rational basis for evidence-based decision-making, both by sponsors throughout their drug development programs and by regulators when sponsors apply for marketing approval.

When planning clinical trials, two considerations are of critical importance. First, the statistical analyses that will eventually be conducted must be planned at the design stage of the study. Second, the desired goal, i.e., approval of a new drug by regulatory agencies, is known from the outset. Regulatory agencies provide enormous amounts of detailed guidance for the conduct and reporting of drug development research. Guidance documents should therefore be studied before starting the drug development program.

J.R. Turner et al., *Cardiovascular Safety in Drug Development and Therapeutic Use*, DOI 10.1007/978-3-319-40347-2_4

4.2 Categorization of Clinical Trials

Clinical trials are often categorized into four phases, with a given trial being identified as belonging to one of them. Traditional descriptions are as follows:

- Phase I: These are pharmacologically oriented studies that typically look for the best dose(s) to employ in subsequent trials. Comparison with other treatments is not the first priority, although a small control group is often included in trial designs. The focus here is on safety.
- Phase II: These trials are usually performed in individuals with the clinical condition of interest, and look for evidence of biological activity, efficacy, and safety.
- Phase III: Comparison with another treatment (which can be a placebo or a different active drug) is a fundamental component of the design of these trials. They are conduced if a sponsor believes that Phase I and Phase II trials have provided preliminary evidence that the new treatment is safe and effective. If the sponsor believes that the entire data set from Phase I, II, and III trials provide compelling evidence of the drug's safety and efficacy, a marketing application will be submitted.
- Phase IV: Phase IV trials are conducted following a drug successfully receiving marketing approval. As the Institute of Medicine of the National Academies (IOM) has stated, "The [marketing] approval decision does not represent a singular moment of clarity about the risks and benefits associated with a drug – preapproval clinical trials do not obviate continuing formal evaluations after approval" (IOM 2007). Along with postmarketing surveillance, a topic addressed in Chap. 14, postmarketing trials are therefore of great importance.

A more informative alternative system of categorization was provided by the ICH: their nomenclature, presented in Table 4.1, is much more descriptive of the nature of a given trial.

4.3 Statistical Significance

For a drug to be given marketing approval by a regulatory agency, regulators must decide that the sponsor has provided compelling evidence of its efficacy as well as its safety. Efficacy is assessed in two ways: the drug must be demonstrated to show statistically significant efficacy and also demonstrated to show clinically significant efficacy. The discipline of Statistics has provided methodologies suitable for both assessments. Assessment of statistical significance is addressed via formalized hypothesis testing requiring the creation of a research question, a research hypothesis, and a null hypothesis. Assessment of clinical significance is addressed via the employment of confidence intervals. In the latter case, the process is less formulaic in that it requires the employment of clinical judgment in conjunction with statistical methodology. However, it is the more important determination. Demonstration

Table 4.1 The ICH categorization of clinical trials

Objective(s) of study	Study examples
Human pharmacology trials	
Assess tolerance Describe or define pharmacokinetics (PK) and pharmacodynamics (PD) Explore drug metabolism and drug interactions Estimate [biological] activity	Dose tolerance studies Single- and multiple-dose PK and/or PD studies Drug interaction studies
Therapeutic exploratory studies	
Explore use for the targeted indication Estimate dosage for subsequent studies Provide basis for confirmatory study design, endpoints, methodologies	Earliest trials of relatively short duration in well-defined narrow patient populations using surrogate of pharmacological endpoints or clinical measures Dose–response exploration studies
Therapeutic confirmatory	
Demonstrate/confirm efficacy Establish safety profile Provide an adequate basis for assessing benefit–risk relationship to support licensing [marketing approval] Establish dose–response relationship	Adequate and well-controlled studies to establish efficacy Randomized parallel dose–response studies Clinical safety studies Large simple trials Comparative studies
Therapeutic use	
Refine understanding of benefit–risk relationship in general or special populations and/or environments. Identify less common adverse reactions Refine dosing recommendation	Comparative effectiveness studies Studies of mortality–morbidity outcomes Studies of additional endpoints Large simple trials Pharmacoeconomics studies

Source: ICH E8: General Considerations for Clinical Trials

of statistically significant evidence of efficacy is a necessary condition for regulatory approval, but it is not a sufficient one: it is perfectly possible for a drug's efficacy to attain statistical significance but not to be considered of clinical significance.

4.3.1 The Role of Probability in Efficacy Assessment

Efficacy evaluations are facilitated by the conduct of a randomized clinical trial that allows the comparison of responses to the drug under development (the test drug) with those to a control drug (a placebo or another active drug). An active control drug is used when it is considered unethical to deny participants in the control drug treatment arm some form of therapy, and in such cases the control drug is often the current standard of care for the indication of interest. The drug's treatment effect, the measure of efficacy, is defined as the mean response of participants who received the test drug minus the mean response of participants who received the control.

Imagine a hypothetical clinical trial comparing an antihypertensive medication with placebo. The mean response to the test drug is a reduction of 10 mmHg in systolic blood pressure (SBP), the endpoint of interest in the trial, and the mean response to the placebo is a mean reduction in SBP of 2 mmHg. The calculation conducted is "10 – 2," yielding a value of 8. The test drug's treatment effect is therefore 8 mmHg.

A very reasonable question arises here. By definition, a placebo is a substance that is not biologically active, and it therefore cannot have had any pharmacological influence on SBP. However, it is a truism of clinical trials that the mean response to a placebo is often a smaller response in the same direction as the response to the test drug. That is, simply being in the clinical trial environment can lead to a small "improvement" in the biological endpoint of interest (the Hawthorne effect). It is therefore accepted practice to define and calculate the test drug's treatment effect in this manner rather than to regard the mean change produced by the test drug as the treatment effect with no consideration being paid to the mean response to the control drug.

Determination of the drug's treatment effect is the first step of the analytical procedure to determine whether the drug's efficacy attains statistical significance. The next step concerns determining the likelihood that a treatment effect of that magnitude (or greater) could have been obtained in the clinical trial by chance alone. If our determination is that it could have occurred by chance alone, we have little faith that we would get a similar result if we were to conduct a similar trial again, and therefore we do not have any degree of reasonable assurance that the drug would be likely to provide that degree of therapeutic benefit to patients if it were to be given regulatory approval. If our determination is that it is sufficiently unlikely that it could have occurred by chance alone, we have a much greater degree of assurance that the drug would likely provide that degree of therapeutic benefit to patients if given regulatory approval.

These considerations lead directly to the realm of probability. Probability is an important component of the analytical strategies utilized in the assessment of statistical significance. One commonly used level of probability in drug development is the 5 % level, a percentage version of odds of one in 20: if the odds of something occurring are one in 20, there is a 5 % chance that it will occur. Consider the following example. You toss a coin and it lands heads up repeatedly: what is the likelihood the coin has heads on both sides? Mathematically, if you toss a normal coin (one side is heads and the other side is tails) once, the chance of it landing heads is 50 %. If you toss it again, the chance of it landing heads up twice in succession is 1 in 4 (25 %). Similarly, the chance of it landing heads up three times in a row is 1 in 8 (12.5 %), four times in a row is 1 in 16 (6.25 %), five times in a row is 1 in 32 (3.13 %), six times is 1 in 64 (1.56 %), and so on. At what stage would you stop the experiment and say that this coin is definitely not normal and the continued occurrence of the coin landing heads up is not due to chance? The greater the number of tosses, the greater your certainty of being correct. However, based on the arbitrarily chosen but widely accepted convention in statistics, you would stop after 5 tosses, since the probability of getting 5 heads in a row is now 1 in 32, i.e., <5 %. This

example also highlights that the level of probability selected to decide if the observations are due to chance can be moved in either direction if such a move can logically be justified.

A probability of 5 % can be expressed as $p = 0.05$. The statement "$p < 0.05$" (i.e., the probability is less than 0.05) means that the probability of something occurring is less than 5 %. Statistical analysis of the data from the hypothetical clinical trial just discussed will provide a probability value associated with the likelihood that a treatment effect of the magnitude attained (or greater) would have resulted by chance alone. Statistical convention states that if the probability value provided by the analysis is less than 5 %, i.e., $p < 0.05$, it is deemed that the magnitude of the treatment effect was not due to chance alone: rather, the size of the treatment effect was directly affected by a systematic influence (discussed further in the next section), and it attained statistical significance. That is, the test drug demonstrated a statistically significantly greater reduction in SBP than did the control drug.

The statement "$p < 0.05$" is likely the most recognized nomenclature in drug development. As an aside here, despite this prominence, the value of 0.05 was not ordained, but was conceived by the visionary statistician Sir Ronald Fisher. Had he decided, for example, that odds of 1 in 25, with an analogous p-value of 0.04, were more appropriate than odds of 1 in 20, modern science might be held to a different standard. Whether the value of 0.05 is "right" (whatever right means) is not the issue here: the important consideration is the acknowledgment that a particular value has been chosen and is honored by all stakeholders in the drug development endeavor.

An additional level of probability of interest is the 1 % level. A probability of 1 % can be expressed as $p = 0.01$. The statement "$p < 0.01$" (i.e., the probability is less than 0.01) means that the probability of something occurring is less than 1 %. If the probability value provided by an analysis is less than 1 %, i.e., $p < 0.01$, the result has attained a higher degree of statistical significance than the 5 % level.

4.3.2 Systematic Influence and Randomization

From the present perspective, therefore, a statistically significant result is regarded as a probabilistic statement that the result obtained was not a chance occurrence: rather, it was caused by a systematic influence on the data collected from the participants in the two treatment groups. The systematic influence of interest is that one group of participants received the drug, and the other group of participants received the control treatment. However, and very importantly, to be able to consider this potential source of influence as the systematic influence leading to the result obtained, it is necessary to mitigate to the greatest extent possible all other potential sources of systematic influence. This is achieved via two processes of key importance to discussions throughout this book: the process of randomization and the implementation of strict experimental control by treating participants in the two

groups in an (ideally) identical manner with the single exception of receiving the test drug or the control drug.

Randomization involves randomly assigning participants to one of the treatment groups so that the many potential influences that cannot be controlled for (e.g., height, weight) or cannot be determined by observation (e.g., specific and relevant genetic influences) are likely to be as frequent in one treatment group as they are in the other. Randomization occurs after an individual's eligibility for a clinical trial has been determined and before any experimental data are collected. Randomization facilitates the random assignment of trial participants to different treatment groups with the intent of avoiding any selection bias. That is, randomization means that potential sources of influence on the data other than receiving the drug treatment or receiving the control treatment have been randomly allocated to each treatment group and therefore cannot exert a systematic influence on the results of the trial.

In statistical nomenclature, the goal of randomization is to eliminate bias. This includes participant bias based on knowledge of which treatment group they have been assigned to and also investigator bias. Investigator bias is eliminated by preventing investigators from deliberately assigning participants to one treatment group or the other. The process of randomization is facilitated by the generation of a randomization list. This list is generated (often by a random-number generator) in advance of recruiting the first participant. The randomization list is generated under the direction of the trial statistician. To maintain the confidentiality necessary for a double-blind trial to be conducted, i.e., a trial in which neither the participants nor the investigators running the trial know which treatments participants are receiving, the list is not released to the trial statistician until the completion of the study.

In many trials, participants have an equal chance of receiving either the drug or control treatment. In these cases, randomization is described as occurring in a 1:1 ratio. Using statistical nomenclature, this ratio provides the most powerful method of determining whether the drug is indeed more effective than the control, and it is typically used in Phase II (therapeutic exploratory) and Phase III (therapeutic confirmatory) trials. However, in other settings, it is legitimate and more informative with regard to the specific aims of a given trial, to use other randomization ratios. For example, a ratio of 2:1 for treatment vs. control means that two-thirds of the participants would be randomized to the treatment group and one-third to the control group. While the statistical power to detect a difference between the groups is not as high as it would be if the number of participants in each group were equal, there is a salient advantage of such a randomization ratio: more safety data concerning the drug will be gained, since two-thirds of the total number of participants in the study will receive this treatment, instead of one-half in the case of a 1:1 ratio. Ratios such as 2:1 and 3:1 for treatment vs. control are often seen in Phase I (human pharmacology) trials. Other randomization ratios are also possible, such as in cases where several doses of a drug are being employed along with a control treatment: in this setting, a ratio of 1:1:1:1 indicates that participants are randomly assigned to one of four groups, e.g., three drug treatment groups (perhaps 10, 20, and 30 mg of the drug) and a control group.

4.3.3 A Case Study: The United Kingdom Medical Research Council's Streptomycin Trial

Credit for conducting the first pharmaceutical randomized clinical trial is often given to a trial that was conducted before the Kefauver–Harris Amendments. The UK Medical Research Council's Trial of Streptomycin for Pulmonary Tuberculosis was conducted by Sir Austin Bradford Hill and his colleagues (the Streptomycin in Tuberculosis Trials Committee, chaired by Dr Geoffrey Marshall) in the late 1940s (MRC Streptomycin in Tuberculosis Trials Committee 1948). The control treatment arm of the trial consisted of the standard of care at the time, which was bed rest. The streptomycin treatment arm consisted of bed rest plus intramuscular administration of 2 g/day of streptomycin, given in four injections at 6-h intervals. While it is true that control groups had been used in medical research prior to this trial, the method of allocating participants to one of two treatment groups had been alternate allocation, simply placing the next individual entering the trial in the alternate treatment group to the one entered by the previous individual (Yoshioka 1998). In this trial, participants were randomized to one of the two treatment arms via reference to a statistical series based on random sampling numbers: details of the series were unknown to any of the investigators or to the study coordinator. Compelling evidence of efficacy was provided, and streptomycin subsequently became the first antibiotic treatment for this disease.

4.3.4 An Illustrative Example of an Efficacy Analysis to Determine Statistical Significance

Clinical trials are conducted to answer a research question. ICH Guideline E8 comments as follows (ICH E8 1997):

> Clinical trials should be designed, conducted, and analyzed according to sound scientific principles to achieve their objectives; and should be reported appropriately. The essence of rational drug development is to ask important questions and answer them with appropriate studies. The primary objectives of any study should be clear and explicitly stated.

For the sake of continuity with the hypothetical trial introduced in Sect. 4.3.1, imagine a sponsor is developing a new drug to lower SBP, i.e., an antihypertensive drug. A clinical trial to investigate the antihypertensive effects of the drug requires a research question. A general question such as "Is this drug good for people's blood pressure?" is not useful in this context. A better research question (which will be refined further in due course) is "Does the new drug alter SBP more than placebo?" Once this research question has been formulated, two hypotheses are created, the research hypothesis and the null hypothesis.

A good research hypothesis has traditionally included four important elements: population, intervention, control, and outcome (PICO for short). More recently, the

question "When?" has also been added on to the outcome, if appropriate. The new research question could be reframed as "Does the new drug alter SBP more than placebo in individuals with mild essential hypertension after 7 days of treatment?" The research hypothesis typically reflects what is "hoped for," which in this case is that the drug undergoing testing will indeed alter SBP. In strict scientific terms, hope has no place in experimental research: the goal is to discover the truth, whatever it may be, and one should not start out hoping to find one particular outcome. In the real world, this ideologically pure stance is not common for many reasons (financial reasons being not the least of them). The research hypothesis would therefore be stated as follows: the new drug alters SBP more than placebo in individuals with mild essential hypertension after 7 days of treatment.

The second hypothesis created is called the null hypothesis, which is the crux of hypothesis testing (it is sometimes presented first for this reason, followed by the research hypothesis, but order is not critical). The null hypothesis states that the new drug does not alter SBP more than placebo in individuals with mild essential hypertension after 7 days of treatment.

The process of hypothesis testing now takes place. Hypothesis testing revolves around two actions following an appropriate statistical analysis: rejecting the null hypothesis and failing to reject the null hypothesis. Statistical methodology necessitates a choice being made here, i.e., it is a forced choice paradigm. One of these two actions—rejecting the null hypothesis or failing to reject the null hypothesis—will occur at the end of all hypothesis testing. The action taken is determined by the statistical significance attained by the test statistic obtained in the statistical analysis.

Consider these results from a randomized, placebo-controlled Phase III trial of an antihypertensive drug. Participants were randomized in a 1:1 ratio to drug or placebo. The first step is to calculate the mean change score for each treatment group: in our ongoing example, these values are a mean decrease in SBP of 10 mmHg for the drug treatment group and a mean decrease in SBP of 2.00 mmHg for the placebo treatment group. The second step is to calculate the drug's treatment effect. As first presented in Sect. 4.3.1, a drug's treatment effect is defined as the mean response to the test drug (here, the antihypertensive) minus the mean response to the control (here, the placebo), and the treatment effect is therefore 8.00 mmHg.

The first point of interest is now established: the drug led to a mathematically greater reduction in SBP than did the control. The important question now becomes whether or not the drug led to a statistically significantly greater reduction in SBP. One form of analysis that is appropriate here is the independent-group *t*-test, an analysis that derives its name from the fact that the participants receiving the test drug were different individuals from the participants receiving the control drug. Analysis of the data will result in a value associated with the test statistic in this particular statistical test, which is called *t*. The magnitude of the test statistic will be associated with a *p*-value, and the magnitude of *t* will have to reach a certain size for the result to attain statistical significance. Imagine that the *p*-value associated with the test statistic is less than 5 %, i.e., $p < 0.05$. We therefore reject the null hypothesis and declare that the result attained statistical significance: this allows us to state that the test drug led to a statistically significantly greater reduction in SBP than the control treatment.

4.3.5 *Factors Influencing the Attainment of Statistical Significance*

As noted in Sect. 4.2, comparison with another treatment (a placebo or an active control) is a fundamental component of the design of Phase III (therapeutic confirmatory trials). In the previous section, we compared data from participants receiving the antihypertensive drug to those from participants receiving placebo. The treatment effect was a reduction in SBP of 8 mmHg, and this result attained statistical significance. Three fundamental aspects of the data set resulting from this trial govern whether or not statistical significance was obtained:

1. Between-groups variation in the data. This is an overall measure of how different participants' reductions in SBP in the drug treatment group are from those for the control group.
2. Within-groups variation in the data. This is a measure of how different the individual reductions in SBP in the drug treatment group are from each other and how different the individual reductions in SBP in the control group are from each other.
3. The total number of SBP reduction values collected in the trial. Since one SBP reduction value was obtained for each participant, this is effectively the total number of participants in the trial.

Consider the basic task being performed by the statistical analysis in these simple terms: we want to know if one group of numbers (SBP reductions in the drug treatment group) is different from a second set of numbers (SBP reductions in the control group). Consider a hypothetical example presented by Turner and Thayer (2001). Group A consists of five numbers and Group B consists of a second set of five numbers:

- Group A: 47, 56, 44, 53, and 50
- Group B: 54, 60, 66, 63, and 57

There are also two other groups of five numbers each:

- Group C: 100, 70, 10, 20, and 50
- Group D: 10, 90, 60, 95, and 45

Let's compare Group A with Group B and also compare Group C with Group D. Simply from visual inspection, do you get the feeling that the group of numbers (data) in Group A is meaningfully different from the data in Group B? Similarly, do you get the feeling that the group of numbers (data) in Group C is meaningfully different from the data in Group D? Looking at Group A and Group B, you may think that numbers in both groups are very close to each other and that, overall, the numbers in Group B tend to be greater than the numbers in Group A since there is little overlap between the two groups. Looking at Group C and Group D, you may think differently, i.e., that there is a lot of overlap, and it is therefore difficult to get a good visual impression of to what degree the two groups differ from each other.

As a next step towards answering these two questions, consider the first two of the three fundamental aspects of a data set presented at the start of this section: between-groups variation in the data and within-groups variation in the data. Between-groups variation is quantified as the difference between the means involved in each of our two comparisons. Consider first the comparison between Group A and Group B. The means of these groups are 50 and 60, respectively, and hence the between-groups variation is 10.

Consider next the within-groups variation, i.e., how different from each other the values in Group A are and how different from each other the values in Group B are. A simple quantification of within-groups variation focuses on the difference between the largest value in a group and the smallest value in the same group, which is called the range. The range in Group A is 12 (56–44) and the range for Group B also happens to be 12 (66–54).

Now compare Group C and Group D in the same manner. The means of Group C and Group D are 50 and 60, respectively, and hence the between-groups variation is 10. The range in Group C is 90 (100–10), and the range in Group D is 85 (95–10).

Next, let's look at the details of the two comparisons just made. For the comparison between Group A and Group B, the between-groups variation is 10. The within-groups variation is represented by ranges of 12 and 12, respectively. For the comparison between Group C and Group D, the between-groups variation also happens to be 10, but the within-groups variation is represented by considerably larger ranges of 90 and 85, respectively.

Now, in addition to simple visual inspection regarding the two comparisons, we have some statistical information to help us to decide whether there is a meaningful difference between the values in Group A and Group B and likewise for Group C and Group D. For each comparison, the between-groups variation has been quantified by a comparison of the means, and in each case the difference between the respective means was 10. Also for each comparison, the within-groups variation was captured by the respective ranges: the ranges for Group A and Group B were both 12, while the ranges for Group C and Group D were considerably greater, i.e., 90 and 85, respectively. While we will not perform the appropriate statistical analysis since this example is illustrative conceptually, and each reader can form his or her own opinion, the authors feel that there is a higher change of regarding Group A and Group B to be meaningfully different than there is of regarding Group C and Group D to be meaningfully different.

Using statistical nomenclature, the arithmetic mean of a group of numbers (the sum of the values divided by the total number of values) is called a measure of central tendency, and it is the two group means that are used to quantify between-groups variation. The range is a measure of spread, or dispersion, of the whole group of values around the group's mean. In practice, a more sophisticated characterization of dispersion is used. Since the range is determined by only two values within the group, the smallest and the greatest, there are three other values in each group in our example that do not contribute to evaluations of within-groups variation. In contrast, other characterizations of dispersion utilize all values within a group. When such characterizations are used, the term variance is appropriate.

Finally in this section, we will revisit all three fundamental aspects of a data set that govern whether or not there is a statistically significant difference (the statistical characterization of the words "meaningful difference" used throughout our example) between two groups of numbers:

1. Between-groups variation in the data. The other two aspects of the data set being equal, the greater the difference between the group means, the greater the chance that the means will be found to be statistically significantly different from each other.
2. Within-groups variation in the data (which we will now call variance). The other two aspects of the data set being equal, the greater the variance, the smaller the chance that the means will be found to be statistically significantly different from each other.
3. The total number of data points in both groups being considered. The other two aspects of the data set being equal, the greater the number of data points, the greater the chance that the means will be found to be statistically significantly different from each other.

4.4 Analyzing Data from Clinical Trials Employing More than Two Treatments

Consider a second hypothetical study in which three doses of a new antihypertensive drug are to be compared, and three groups of participants will each receive one dose. Such a study may be performed in earlier-phase drug development to determine the most appropriate dose for subsequent larger trials. The research question, research hypothesis, and null hypothesis in this case would be:

- Research question: Does the dose of drug administered statistically significantly influence the change in SBP seen for the different doses?
- Research hypothesis: The dose of drug administered statistically significantly influences the change in SBP seen for the different doses.
- Null hypothesis: The dose of drug administered does not statistically significantly influence the change in SBP seen for the different doses.

The simple fact that there are more than two treatment groups means that the independent-group *t*-test introduced in Sect. 4.3.4 cannot be employed; that test can only be employed when there are two treatment groups. In this case, an independent-group analysis of variance (ANOVA) is appropriate, since this analytical approach can encompass data from more than two groups.[1] The test statistic in an ANOVA is

[1] It should be noted that ANOVA can also be used when there are only two treatment groups. If one analyzed the same data set with an independent-group *t*-test and then with an independent-group ANOVA, the *t* statistic and the *F* statistic would be different numbers, but the p-value associated with each of them, i.e., the key value of interest in determining the attainment of statistical significance, would be identical.

called *F*, a name that pays respect to Sir Ronald Fisher, the statistician who developed this approach. Analogously to the test statistic *t* that results from a *t*-test, the test statistic *F* that results from an ANOVA has to reach a certain size to attain statistical significance. That is, the magnitude of the test statistic *F* will be associated with a *p*-value, and the magnitude will have to reach a certain size for that *p*-value to be less than 5 %, i.e., for the result to attain statistical significance.

In this hypothetical clinical trial, three groups of 20 participants receive one dose of an antihypertensive drug, 10, 20, or 30 mg. The mean decreases in SBP for the three dose treatment groups are as follows:

- 10-mg dose treatment group: 3 mmHg
- 20-mg dose treatment group: 11 mmHg
- 30-mg dose treatment group: 12 mmHg

Imagine that the calculated test statistic *F* is 4.0 and that the magnitude of *F* is sufficiently great that the associated *p*-value is less than 5 %, i.e., $p < 0.05$. Statistical significance is therefore attained, the null hypothesis is rejected, and it is concluded that the dose of drug administered statistically significantly influences the change in SBP.

However, this statement in itself does not tell us anything about the mean decreases in SBP for the three drug dose treatment groups. To address this, the mean decreases in SBP for the three groups need to be considered. The mean decrease for the 10-mg dose treatment group (3 mmHg) was the least, the mean decrease for the 20-mg dose treatment group (11 mmHg) was numerically greater, and the mean decrease for the 30-mg dose treatment group (12 mmHg) was numerically greater than both of the other two dose treatment groups. However, even this additional consideration does not provide the most comprehensive answer possible in this situation. In this context of more than two treatment groups, the ANOVA is called an omnibus test. It is an overall test of statistical significance, but it does not reveal which of several possible patterns of statistically significant differences has occurred. The statistically significant result says that, somewhere, there is at least one statistically significant difference between pairs of the dose treatment groups. There are three pairs of dose treatment groups to consider:

- The 10-mg dose treatment group and the 20-mg dose treatment group
- The 10-mg dose treatment group and the 30-mg dose treatment group
- The 20-mg dose treatment group and the 30-mg dose treatment group

Given the carefully chosen mean changes used in this hypothetical example, simple visual inspection may suggest that the 10-mg dose treatment group mean (a decrease in SBP of 3 mmHg) and the 20-mg dose treatment group mean (a decrease of 11 mmHg) may be meaningfully different and also that the 10-mg dose treatment group mean (a decrease of 3 mmHg) and the 30-mg dose treatment group mean (a decrease of 12 mmHg) may also be meaningfully different. The same visual inspection may also suggest that the 20-mg dose treatment group mean (a decrease of 11 mmHg) and the 30-mg dose treatment group mean (a decrease of 12 mmHg) may not be meaningfully different. However, in reality, the pattern of

dose treatment group patterns is likely to be less sharply defined. Additionally, whether the pattern of dose–response across treatment groups is relatively clear or not in a visual inspection, such inspection does not provide a statistical answer to the question of interest, i.e., which dose treatment group(s) differ significantly from which other dose treatment group(s). We therefore need a further statistical analysis.

4.4.1 A Further Analytical Step: Multiple Comparisons

The attainment of statistical significance described in the preceding section revealed that there is at least one statistically significant difference between a pair of dose treatment groups. However, given that there are more than two groups, the omnibus test cannot reveal the precise pattern of statistical significance by itself. Multiple comparison techniques are tests that facilitate the comparison of the means of each pair of treatment groups to see which pair(s) differ statistically significantly from each other. Multiple comparisons therefore provide a more detailed understanding of data than is provided by the initial omnibus test. (In cases where an omnibus test yields a nonsignificant result, it is not appropriate to continue to perform multiple comparisons.)

One multiple comparison strategy that is appropriate in this illustrative hypothetical study is the Tukey test. The first step in the Tukey test is to construct a trellis for the comparison of all sample means (Fowler et al. 2002), which is presented in Table 4.2. For each pair of comparisons, the mean of one dose treatment group is subtracted from the mean of the other. The sign (positive or negative) of the individual means must be taken into account in these calculations, but if the sign of the resulting difference is a negative sign, this can be ignored. Therefore, either mean can be subtracted from the other, since the resultant absolute value will be identical in both scenarios. Since the mean SBP changes for all three dose treatment groups in the example are actually decreases in SBP, negative signs are used in Table 4.2. For the comparison of the 10-mg group and the 20-mg group, the necessary calculation is

$$(-3)-(-11)=-3+11=8.$$

The other two calculations are performed similarly and the resulting differences placed into the trellis.

Next, the test statistic for this test is calculated. This test statistic used in this analysis is represented by the capital letter *T*. This test statistic is then used as a

Table 4.2 Trellis for the Tukey multiple comparison test

Dose treatment group and group mean	20 mg (−11 mmHg)	30 mg (−12 mmHg)
10 mg (−3 mmHg)	8	9
20 mg (−11 mmHg)	N/A	1

reference standard against which to compare each of the three differences between the means of pairs of groups presented in the trellis. Imagine that the value of T is calculated as 1.70. In this test, any value that is greater than the test statistic T is defined as being statistically significant at the 5 % level. The results are therefore:

- 10-mg dose treatment group vs. 20-mg dose treatment group = 8; $p < 0.05$
- 10-mg dose treatment group vs. 30-mg dose treatment group = 9; $p < 0.05$
- 20-mg dose treatment group vs. 30-mg dose treatment group = 1.

These results now provide the full numerical answer to the original research question. As always, the numerical results need to be interpreted in words in the context of the specific study. This interpretation requires combining the information from the Tukey test with the group means calculated earlier:

- There is evidence at the 5 % level that the mean SBP decrease for the 20-mg dose treatment group is significantly greater than the mean decrease for the 10-mg dose treatment group.
- There is evidence at the 5 % level that the mean SBP decrease for the 30-mg dose treatment group is significantly greater than the mean decrease for the 10-mg dose treatment group.
- There is no statistical evidence that the mean SBP decrease for the 30-mg dose treatment group is significantly greater than the mean decrease for the 20-mg dose treatment group. (Note that this statement is made even though the mean SBP decrease for the 30-mg dose treatment group was actually numerically greater than that for the 20-mg dose treatment group.)

A key question at this point is the following: Since each comparison in the Tukey test involves only two groups, and since we have already encountered a test that compares two groups perfectly adequately (the *t*-test), why not simply conduct three *t*-tests, one for each pair of groups that need to be compared? The answer to this question concerns a potential problem when conducting more than one comparison, i.e., conducting multiple comparisons. As long as the appropriate statistical care is taken, the problem can be dealt with completely satisfactorily. However, simply performing three *t*-tests would not fulfill this criterion of taking appropriate statistical care. The more comparisons that are made, the more likely it becomes that a statistically significant result will erroneously be "found" by chance alone. This occurrence is called a type I error. In statistical terminology, when adopting the 5 % significance level, we are setting alpha at 0.05: that is, $\alpha = 0.05$. Table 4.3 presents the maximum probability of committing a type I error when multiple hypotheses are tested at $\alpha = 0.05$. As can be seen, the maximum probability of committing a type 1 error when making three comparisons has risen from 5 % (the level deemed acceptable when making one comparison) to 14.3 %.

The Tukey test that was employed in our hypothetical example is structured to take a conservative approach in an ingenious manner. Keeping all other considerations and variables constant, as the number of treatment groups increases (i.e., as the number of comparisons being made increases), the size of the test statistic T increases. Since the difference between any two groups' means has to exceed the

Table 4.3 Maximum probability of committing a type I error when each of multiple hypotheses is tested at $\alpha = 0.05$

Number of hypotheses tested at $\alpha = 0.05$	Maximum probability of committing a type 1 error
1	0.050
2	0.098
3	0.143
4	0.185
5	0.226
6	0.265
7	0.302
8	0.337
9	0.370
10	0.401
15	0.537
20	0.642

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value of *T* for that test to attain statistical significance, the total number of comparisons being made determines the likelihood of that difference between the two groups' means attaining statistical significance. For a difference score of a given magnitude, the more comparisons that are made, the less likely it is that the difference will attain statistical significance.

Another approach to multiple comparisons is the Bonferroni test. The strategy in this case is to divide α (typically 0.05 when a single comparison is being made) by the number of tests conducted following a significant omnibus ANOVA test. Hence, if ten comparisons were to be made, the α-level used for each comparison would become 0.05/10, i.e., 0.005, a considerably more conservative value.

4.4.2 Type I and Type II Errors

The previous section introduced the concept of type I errors, which occur when statistically significant results are erroneously "found" by chance alone. There is also a type II error. This occurs when a statistically significant difference that truly exists is not found. Ideally, the likelihood of either types of error would be zero, or at least as low as possible. In reality, the possibility of making these errors cannot totally be eliminated, but their likely occurrence can be balanced one against the other.

Consider the implications of these errors at the end of a clinical trial. When a type I error (also known as a false positive) occurs, the researchers reject the null hypothesis, e.g., they "find" statistically significant efficacy when it did not truly exist. The inference from this finding, based on the sample of participants employed in this trial, is that the drug would be effective in the population from which the sample was chosen. This likely would not be the case. When a type II error

Table 4.4 Type I and type II errors and their consequences

	Reality	
Action based on study results	Research hypothesis is true	Null hypothesis is true
Reject null hypothesis	Correct action	Type I error (false positive)
Fail to reject null hypothesis	Type II error (false negative)	Correct action

(also known as a false negative) occurs, the researchers fail to reject the null hypothesis, i.e., fail to find statistically significant efficacy that truly exists. The inference from this finding, based on the sample of participants employed in this trial, is that the drug would not be effective in the population from which the sample was chosen. Again, this likely would not be the case. These scenarios are summarized in Table 4.4.

4.4.3 Well-Defined Study Objectives and Endpoints

All of the studies that are performed before a therapeutic confirmatory trial is started collect information that facilitates a logical scientific progression from human pharmacology studies to the point where conduct of a therapeutic confirmatory trial is appropriate. In a real sense, all of these studies, and all of the information gained to date, have had one purpose: to allow the primary objective in the therapeutic confirmatory trial to be stated as simply as possible. In this context, the word "simple" is not pejorative. To the contrary, a primary objective that can be stated simply can be tested simply, i.e., in a straightforward and unambiguous manner. This is a highly desirable attribute in a primary objective.

The number of objectives that should be incorporated in any clinical trial is often a topic of considerable debate among study teams. One argument often propounded is that, while undertaking the considerable demands of conducting a therapeutic confirmatory trial, why not collect as much data as possible and ask as many questions as possible? This approach leads to a large number of study objectives, sometimes broken down into primary objectives, secondary objectives, and even tertiary objectives. Proponents of this approach see it as commendable to have all of these objectives specified a priori, since this removes the possibility of any later intimation that these topics of interest arose after the data were analyzed according to the study's statistical plan, i.e., they were post hoc analyses. However, this approach leads to serious statistical problems, and it can compromise the weight of any particular piece of evidence that is presented to regulatory agencies.

The previous section discussed the concerns that accompany multiple comparisons, i.e., the issue of multiplicity. In the context of study objectives, the greater the number of objectives presented in a study protocol, the greater the number of comparisons that will be made at the analysis stage, and the greater the chance of a type I error. As Machin and Campbell (2005) commented, "If there are too many end-

points defined, the multiplicity of comparisons then made at the analysis stage may result in spurious statistical significance."

By the time a therapeutic confirmatory trial is appropriate, it should be possible to state a single primary objective (or perhaps two if the sponsor really feels that this is appropriate) that is clinically relevant and biologically plausible. It is not our intention to minimize the difficulty of choosing just one or two primary objectives, but rather to emphasize the importance of doing so. Machin and Campbell (2005) suggested that, in cases where additional evaluations are included in addition to the primary (more clinical) endpoints, study design should focus on the few key endpoints. In turn, at the analysis stage, these endpoints provide the focus for rigorous statistical analysis and interpretation. Any secondary endpoints included in the study protocol might be summarized and less formal statistical comparisons made for them.

In conclusion for current discussion of multiple comparisons (discussions will resume in Chap. 5), it is not appropriate statistical practice to conduct many tests, find one statistically significant result, and present this lone result as a noteworthy finding. It is particularly not appropriate to present this result in the spirit that this is something that was anticipated before the study was conducted (i.e., that this was identified a priori as a comparison of interest). If a situation occurs in which one of many tests is significant, and it is believed that the result is biologically plausible and worthy of further investigation, a subsequent trial needs to be conducted, and this comparison needs to be identified in the study protocol as the primary comparison of interest.

4.5 Clinical Significance

As noted previously, demonstration of statistically significant evidence of efficacy is a necessary condition for regulatory approval, but it is not a sufficient one: it is perfectly possible for a drug to evidence statistical significance but not clinical significance. Gardner and Altman (1986) commented that "presenting *p*-values alone can lead to them being given more merit than they deserve. In particular, there is a tendency to equate statistical significance with medical importance or biological relevance." Statistical significance must not be equated with medical importance or biological relevance. Therefore, in cases where a statistically significant result is obtained, the next step is to proceed to evaluation of clinical significance. Evaluation of clinical significance is performed via the placement of confidence intervals around a drug's treatment effect as calculated during efficacy analysis, which from this time forward is referred to as the treatment effect point estimate. Confidence intervals facilitate quantification of the degree of confidence that is placed in the treatment effect point estimate. Presentation of confidence intervals as well as the magnitude of a treatment effect point estimate and its degree of statistical significance (the *p*-value attained) is an important component of regulatory documentation and clinical communications.

4.5.1 Confidence Intervals

When a randomized clinical trial is conducted, the group of individuals participating in the trial is a sample chosen from the population of all possible individuals with the disease or clinical condition of interest. Analysis of the trial's data provides a precise result for that particular sample. However, while the sample can contain several thousand participants randomized to the different treatment groups, for many diseases this can be a (very) small percentage of the population from which that sample was chosen. Had a different sample of participants been chosen, the chances of the data obtained being identical is so infinitesimally small that it can be safely said that they would be different. The question of importance here is: How different would they likely be? Ideally, we would like them to be extremely similar, thus providing a result that is extremely similar to the result of the original trial; the more similar the results from a second trial, the more confidence we can reasonably place in the results from the original trial.

An alternate way to conceptualize this point is to note that the ultimate purpose of the results from a specific clinical trial is not to tell us precisely what happened in that trial, but, in combination with results from other trials in the drug's clinical development program, to gain insight into likely drug responses in patients who may be prescribed the drug should it subsequently be approved for marketing.

While the word "confidence" used a few moments ago occurs in its everyday use, the term is also used in Statistics in a precise manner, analogously to the statistical term "significant." A two-sided confidence interval (the abbreviation CI is used when presenting values) constitutes a range of values that are defined by the lower limit and the upper limit of the interval. In the current context, these limits lie symmetrically on either side of the treatment effect point estimate. The confidence interval is defined as a range of values that is likely to cover the true but unknown population treatment effect with a specified degree of certainty. Confidence intervals allow statements concerning the true but unknown population treatment effect to be made with specified degrees of certainty based on the data collected in a single clinical trial.

One of the basic principles of clinical research is to rigorously test the research hypothesis in a small group of participants, for example, in the current context, individuals with hypertension. At the end of the study, the results are then generalized to all patients with the hypertension (the population of interest). This extrapolation of the observations from the sample to the population is conducted via the employment of a statistical estimate called the confidence interval. To extrapolate the sample mean (e.g., 8 mmHg) to the population, one determines the 95 % confidence limits of the sample mean (e.g., 6.5 and 9.5 mmHg). Now, we can predict that with 95 % certainty that the population mean will lie within the range of 6.5–9.5 mmHg. The 95 % confidence limits also have another important implication. If we repeat the same study 100 times, in at least 95 of the 100 studies, the mean will have values between 6.5 and 9.5 mmHg. Since the sample in any study is drawn from a large

population, the larger the sample size, the closer the sample mean will be to the population mean, and therefore the confidence limits of the sample mean will be narrower. In an extreme situation when the sample size is equal to the population, the sample mean will be the same as the population mean.

A commonly used confidence interval is the two-sided 95 % confidence interval, and so this confidence interval is used here, and discussions continue to use the hypothetical example presented earlier in this chapter. The treatment effect used in the example, which is now referred to as the treatment effect point estimate, was 8.00 mmHg. The calculations performed yield a value that is subtracted from the treatment effect point estimate to give the lower limit of the confidence interval and added to the treatment effect point estimate to give the upper limit. Therefore, in this setting, the lower and upper limits of the confidence interval lie symmetrically around the treatment effect point estimate. Imagine that the two-sided 95 % confidence interval has a lower limit of 6.5 mmHg and, therefore, an upper limit of 9.5 mmHg. The result is typically written as follows:

- Treatment effect point estimate and two-sided 95 % CI = 8.00 (6.5, 9.5)

The lower and upper limits define a range of values that we are 95 % confident will cover the true but unknown population treatment effect and allow the following statement to be made:

- The data obtained from this single clinical trial are compatible with a treatment effect in the general population as small as 6.5 mmHg and as large as 9.5 mmHg, and our best estimate is 8.00 mmHg.

The question of importance now is: Does this result provide compelling evidence of clinically significant efficacy? The process of determining clinical significance is not as formulaic as determining statistical significance: in addition to statistical analyses, it requires skilled clinical judgment. The question just asked can be reframed as follows: If approved, is this drug likely to confer therapeutic benefit to patients? The answer requires clinical judgment, and it requires inspection of the lower and upper limits of the confidence interval, with a particular focus on the lower limit. Consider first the upper limit. Is it clinically relevant, i.e., clinically significant, to reduce SBP by 9.5 mmHg? The clinicians involved in the drug's development program may decide that the answer is yes. Consider next the lower limit. Is it clinically relevant, i.e., clinically significant, to reduce SBP by 6.5 mmHg? The clinicians involved in the drug's development program may again decide that the answer is yes. If so, the drug's efficacy is deemed to be clinically significant.

Consider now a different scenario. Imagine a different trial of a similar design in which the treatment effect point estimate was also 8.00 mmHg, but the two-sided 95 % confidence interval has a lower limit of 2.5 mmHg and, therefore, an upper limit of 13.5 mmHg. The result would be written as follows:

- Treatment effect point estimate and two-sided 95 % CI = 8.00 (2.5, 13.5)

The lower and upper limits define a range of values that we are 95 % confident will cover the true but unknown population treatment effect and allow the following statement to be made:

- The data obtained from this single clinical trial are compatible with a treatment effect in the general population as small as 2.5 mmHg and as large as 13.5 mmHg, and our best estimate is 8.00 mmHg.

Again, the question of importance is: Does this result provide compelling evidence of clinically significant efficacy? The magnitude of SBP reduction represented by the upper limit, i.e., 13.5 mmHg, is likely to be judged by the clinicians involved in the drug's development program as clinically significant. Is this likely to be the case for the magnitude of SBP reduction represented by the lower limit, i.e., 2.5 mmHg? This is a more challenging question and is the key question in this context. While any degree of reduction in blood pressure is theoretically desirable, from a practical perspective, a drug that may (only) reduce SBP by 2.5 mmHg in patients if it were to receive marketing approval may not be considered a useful drug by the sponsors' clinicians since there are already drugs approved that lower SBP by considerably greater amounts. If they came to that decision, they might decide to investigate using a higher dose of the drug, or to terminate the drug's development program and transfer the sponsors' resources to pursuing development of other drugs.

This second scenario highlights the difference between statistical and clinical significance. Evidence of the hypothetical drug's statistically significant efficacy was obtained, but compelling evidence of its clinical significance was not. While this can initially appear a strange occurrence, it highlights a critical distinction in drug development: statistical significance does not equate to clinical significance. One way to conceptualize the difference is to regard statistical significance as addressing the reliability of the treatment effect: in this example, there is compelling evidence that the drug, if approved, would lower SBP more than placebo. In contrast, clinical significance utilizes the magnitude of the treatment effect to determine the likely therapeutic benefit of the drug. Since regulatory authorities need to determine that a drug is reliably likely to deliver a certain degree of therapeutic benefit if approved, compelling evidence of both statistical and clinical significance is needed.

4.5.2 Other Confidence Levels of Interest

Two other confidence intervals of potential interest are the two-sided 90 % confidence interval and the two-sided 99 % confidence interval. Placing a confidence interval around a treatment effect point estimate allows the following statement to be made, where "XX%" can be replaced by 90, 95, or 99 %:

- The two-sided XX% CI placed around the treatment effect point estimate obtained from this single trial is a range of values that we are XX% confident will cover the true but unknown population treatment effect.

The widths of the three confidence intervals placed around the same treatment effect point estimate will differ:

- The 90 % CI will be the narrowest.
- The 95 % CI will be wider than the 90 % CI and narrower than the 99 % CI.
- The 99 % CI will be the widest.

To move from having 90 % confidence that the range of values between the lower and upper limits of the confidence interval covers the true but unknown population treatment effect to having 95 % confidence that it does so, the range of values must be greater. The same logic applies when moving from having 95 % confidence to 99 % confidence.

4.5.3 One-Sided Confidence Intervals

As just seen, when using a two-sided confidence interval, interest lies with both the lower and the upper limit. In contrast, a one-sided confidence interval focuses on the placement of a single interval on one specified side of the treatment effect point estimate. In certain circumstances, interest lies with a drug response in one direction only. In these cases it is legitimate to calculate and present a single limit, which is usually referred to as the lower bound of the confidence interval (when placed below the treatment effect point estimate) or the upper bound when placed above it.

It must be clarified and emphasized here that the upper bound of a one-sided 95 % CI will not fall at the same place above the treatment effect point estimate as the upper limit of a two-sided 95 % CI. The upper bound of a one-sided 95 % CI will fall at the same place as the upper limit of a two-sided 90 % CI. It is vital to be clear about precisely what type of confidence interval has been calculated and presented when reporting the results of a clinical trial.

4.5.4 Relationship Between Confidence Intervals and Probability Levels

Confidence intervals are intimately related to probability levels since levels of statistical significance can be deduced from the values of the limits of two-sided confidence intervals. In the scenario we have discussed so far in this chapter, if the two-sided 95 % CI excludes zero, the difference will attain significance at the $p < 0.05$ level. Imagine this hypothetical result:

- 95 % CI = 3.00 (1.08, 4.92)

Both the lower and the upper limits lie above zero, and hence the confidence interval excludes zero. This statement therefore also tells us that the mean reduction

in SBP caused by the drug was statistically significantly greater than that caused by the control. Similarly, if a two-sided 99 % CI does not contain zero, the difference will attain significance at the $p < 0.01$ level.

This relationship between confidence intervals and probability levels arises from the fact that, in the scenario of interest here, i.e., the possible difference in mean responses to two treatments, the "null value" is zero. That is, the treatment effect point estimate that would result if the two group means did not differ at all is zero. Thus, if the 95 % CI excludes zero, there is compelling evidence at the 5 % level that the effect size is not zero, which means that there is compelling evidence that the treatment group means differ. Similarly, if the 99 % CI excludes zero, there is compelling evidence at the 1 % level that the effect size is not zero, which means that there is even stronger evidence that the treatment group means differ. To state the same in reverse, if the 95 % CI includes zero, then we cannot exclude the possibility that there is no difference in responses in the two treatments with 95 % certainty.

4.6 Noninferiority Trials

The study design and analytical strategies discussed to this point in the chapter relate to superiority trials. As the name suggests, the goal is to determine whether or not there is compelling evidence that the drug of interest leads to statistically significantly greater efficacy than the control treatment and, if so, that the degree of efficacy conferred by the drug is clinically significant. We have seen how *t*-tests and ANOVA can be used to determine statistical significance, and confidence intervals can be used to determine clinical significance. Another study design of importance is the noninferiority trial, the topic of this section. Discussion is adapted from Turner and Durham (2015).

While a drug's efficacy is of considerable interest, other factors influence its suitability for therapeutic use and the degree to which it will be successful in the marketplace if approved. These factors include the drug's tolerability, its safety profile (and hence, in combination with its efficacy, the overall benefit–risk profile), and increasingly its cost: cost is influential in the extent to which its use may be reimbursed by payers and hence the degree to which it may be prescribed.

Consider a hypothetical example in which the safety profile of a new drug is dramatically better than that of an existing (reference) drug for the same indication, which would typically be the existing gold standard treatment for the disease of interest. In this case, we may be prepared to accept a certain degree of reduced efficacy since, despite this reduced efficacy, the overall benefit–risk balance of the new drug may be considerably more favorable. We therefore need to decide if we are prepared to accept a certain degree of reduced efficacy since the advantage of a much better safety profile may outweigh a degree of reduced efficacy in the determination of the drug's benefit–risk balance. If we are prepared to do this, we then need to decide precisely what degree of reduced efficacy will be acceptable. If the

new drug has only this degree, or less than this degree, of reduced efficacy, it will be declared noninferior to the reference drug. That is, the goal of a noninferiority trial is to look for compelling evidence that a new drug's efficacy is "acceptably worse" than (noninferior to) that of the reference drug. This degree is captured by the noninferiority margin.

4.6.1 The Noninferiority Margin

The first step in this methodology is defining the noninferiority margin, for which clinical judgment is necessary. This decision must be made before the trial is conducted and the noninferiority margin included in the study protocol since it is a key component of the study's design. In keeping with other hypothetical examples, we will choose a new antihypertensive drug. The clinicians on the study team must choose the noninferiority margin. Given the drug's improved safety profile, imagine that the study team decides that a decrease in mean efficacy of 3.0 mmHg in SBP is acceptable. This choice means that the noninferiority margin will have a value of 3.0 mmHg. Once the trial has been completed, the second step is the employment of an appropriate statistical test.

4.6.2 Hypothesis Construction and Testing

Unlike superiority trials, for which *p*-values are employed to determine if a new drug's efficacy is statistically significantly superior to that of the comparator drug, *p*-values are not typically used in noninferiority trials. Establishing noninferiority is based on the use of confidence intervals.

ICH Guideline E9 (ICH 1998) stated that a one-sided confidence interval should be employed in this context. In the two hypothetical case studies presented, attention falls on the upper limit, or bound, of the commonly chosen one-sided 95 % CI. The reason that the lower bound is not of interest has two parts: (a) if the new drug's efficacy actually turns out to be *greater* than that of the reference drug, that would be a perfectly acceptable outcome that would still lead to the drug being declared noninferior to the reference drug; and (b) this is a true statement no matter how much better its efficacy, and we therefore do not need a specific bound to be placed below the noninferiority margin.

As for a superiority trial design, there will be a research question, a research hypothesis, and a null hypothesis. However, these will be phrased quite differently from those for a superiority trial. They are as follows:

- Research question: Is the new drug noninferior to the reference drug?
- Null hypothesis: The new drug is inferior to the reference drug.
- Research hypothesis: The new drug is noninferior to the reference drug.

The calculated confidence interval will determine whether the null hypothesis is rejected in favor of the research hypothesis or whether we will fail to reject the null hypothesis. The location of the upper bound of the 95% CI that is placed around the treatment effect point estimate, calculated as mean reduction in SBP for the new drug minus mean reduction in SBP for the reference drug, determines whether or not the null hypothesis is rejected. If the value of the upper bound is less than 3.0 mmHg (the value of the noninferiority margin), the null hypothesis will be rejected, and it will be declared that the new drug is noninferior. Conversely, if the upper bound is 3.0 mmHg or greater, we fail to reject the null hypothesis and the new drug will not be declared noninferior; rather, it will be considered inferior.

4.6.3 Case Study 1: Noninferiority Established for New Drug A

Imagine the results from a hypothetical noninferiority trial involving New Drug A. The mean SBP response for New Drug A was a reduction of 8.5 mmHg, written algebraically as −8.5 mmHg. The mean SBP response for the reference drug was a reduction of 10.0 mmHg, written as −10.0 mmHg. The treatment effect point estimate, calculated as the mean new drug response minus the mean reference drug response, is therefore 1.5 mmHg (the calculation is −8.5 minus −10.0, which is equivalent to −8.5 plus 10.0, which is 1.5). That is, New Drug A lowers SBP on average 1.5 mmHg less than the reference drug.

The upper bound of 95% CI is then calculated and placed around the treatment effect point estimate. Imagine that this value is 1.9 mmHg. This is the value of key importance. Since it is less than the value of our noninferiority margin, i.e., 3.0 mmHg, the null hypothesis is rejected in favor of the research hypothesis, and New Drug A is declared to be noninferior to the reference drug: the degree of reduced efficacy associated with the new drug is considered to be "acceptably worse" compared with the reference drug since the new drug offers other salient advantages.

Using different nomenclature, the decision made following the conduct of this noninferiority trial can be explained in these terms. When conducting any type of preapproval clinical trial, the goal is not just to determine how the specific individuals who participated in the trial responded, but to obtain a meaningful estimate of what may be seen if the drug were to receive marketing approval and then be used in the general population of individuals with the disease of interest. Confidence intervals enable such estimation. In this case, the following statement can be made:

> While our best estimate of the reduction in efficacy in the general population for New Drug A is 1.5 mmHg, the data from this single trial are compatible with a reduction in efficacy as great as 1.9 mmHg.

4.6.4 Case Study 2: Noninferiority Not Established for New Drug B

Imagine now the results from a hypothetical noninferiority trial involving New Drug B. As for the trial involving New Drug A, the mean SBP response for the reference drug was a reduction of 10.0 mmHg, written algebraically as −10.0 mmHg. The mean SBP response for New Drug B was a reduction of 7.2 mmHg, written as −7.2 mmHg. The treatment effect point estimate, again calculated as the mean new drug response minus the mean reference drug response, is therefore 2.8 mmHg (the calculation is −7.2 minus −10.0, which is equivalent to −7.2 plus 10.0, which is 2.8). That is, New Drug B lowers SBP on average 2.8 mmHg less than the reference drug.

The upper bound of 95 % CI is then calculated and placed around the treatment effect point estimate. In this case, say that the value is 3.4 mmHg. Again, this is the value of key importance. Since this is greater than the value of our noninferiority margin, i.e., 3.0 mmHg, we fail to reject the null hypothesis, and hence New Drug B is declared inferior to the reference drug. (Note that we make this decision even though the treatment effect point estimate itself lies *below* the noninferiority margin.) That is, the degree of reduced efficacy associated with the new drug is considered to be *unacceptably* worse compared with the reference drug despite the other salient advantages of the new drug: on balance, those advantages do not outweigh its inferior efficacy. In this case the following statement is made:

> While our best estimate of the reduction in efficacy in the general population for New Drug B is 2.8 mmHg, the data from this single trial are compatible with a reduction in efficacy as great as 3.4 mmHg.

4.6.5 Employment of Noninferiority Margins in Proarrhythmic Safety Assessments

In the context of proarrhythmic cardiac safety, a noninferiority margin is employed in the Thorough QT/QTc Study, a clinical trial that is discussed in an introductory manner in the following chapter and then addressed in more detail in Chap. 7. Briefly, the extent of QT prolongation (measured in milliseconds, or msec) seen with a new drug is compared with that seen with placebo. The noninferiority margin in this case is 10 msec. If the one-sided 95 % confidence bound above the difference in QT prolongation between the drug and placebo (i.e., the treatment effect) exceeds 10 ms, the drug is considered “unacceptably worse” than placebo, and its potential to cause cardiac arrhythmias requires additional evaluation in subsequent studies.

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Chapter 5

Analyzing and Reporting Safety Data

Generally speaking, the safety evaluation of new drugs is intended to detect quantifiable effects in as many organs and bodily systems as possible, hence the expression "casting a wide net." However, in the domain of cardiovascular safety, hypothesis-testing approaches are employed to investigate cardiovascular adverse events of special interest.

5.1 Introduction

The previous chapter provided examples of statistical analyses that are used to assess efficacy in clinical trials. In this and the following chapter, the focus moves to assessments of safety. As will be seen in the first part of this chapter, general safety assessments are conducted quite differently from those for efficacy, in that descriptive statistics are used as opposed to hypothesis testing. However, in the domain of cardiovascular safety, hypothesis-testing approaches are employed to investigate the potential occurrence of specific cardiac and cardiovascular adverse events. In the language introduced in this chapter, these can be regarded as adverse events of special interest.

5.2 FDA's Premarketing Risk Assessment Guidance

The FDA's premarketing risk assessment Guidance for Industry discussed the generation, acquisition, analysis, and presentation of premarketing safety data (FDA 2005). To maximize the information gained from clinical trials, the FDA recommends that, from the outset of development, sponsors pay careful attention to the overall design of safety evaluation. The agency is fully aware that "Even large clinical development programs cannot reasonably be expected to identify all risks associated with a product," and it is therefore expected that "some risks will become apparent only after approval, when the product is used in tens of thousands or even millions of patients in the general population" (FDA 2005, p. 6). Nonetheless, the FDA also acknowledges that the larger and more comprehensive the preapproval database, the more likely it is that serious adverse events will be detected during preapproval drug development.

J.R. Turner et al., *Cardiovascular Safety in Drug Development and Therapeutic Use*, DOI 10.1007/978-3-319-40347-2_5

Several factors influence the determination of the appropriate size of a preapproval safety database for a new investigational drug:

- Its novelty, i.e., whether it represents a new mechanism of action or one similar to that of another available treatment(s)
- The condition being treated and the intended population for whom the treatment will be prescribed if approved
- The intended duration of use
- The availability of alternative therapies and the relative safety of those alternatives as compared with the new drug's safety profile

The fact that assessment of both benefit and risk is needed for benefit–risk analysis has a direct impact on the quantity and quality of the safety database. Generally speaking, the greater the drug's benefits, the greater the degree of uncertainty about its safety that will be acceptable and the smaller the safety database that is warranted. (That said, even "smaller" safety databases are extremely large.) Conversely, the fewer the drug's benefits, the less the uncertainty that may be acceptable with regard to its safety and the greater the safety database that is warranted. Additionally, a larger safety database may be appropriate if a drug's nonclinical assessment or human pharmacology studies have identified signals of risk that warrant considerable clinical safety data to define the risk in an adequate manner.

The FDA recommends that sponsors address the potential for serious adverse effects in various categories for all new small-molecule drugs, including the following:

- Drug-related QT interval prolongation
- Drug-related liver toxicity
- Drug-related nephrotoxicity
- Drug-related bone marrow toxicity
- Drug–drug interactions
- Polymorphic metabolism

The meaning of the word "address" in this context varies with circumstance. For example, for a drug that is intended to be applied topically, if it has been demonstrated that the drug has no systemic bioavailability, systemic toxicities would not be of concern, and addressing this issue could therefore be done in relatively less detail.

Temporal relationships between exposure to a drug and the occurrence of an adverse event can be very informative: when preparing individual participant safety reports, the temporal relationship between drug exposure and an adverse event is a critical consideration in the assessment of potential causality (FDA 2005). However, temporal parameters such as time to event and the duration of the event can be overlooked in aggregate inspections of safety data. As noted in the guidance, "Simple comparisons of adverse event frequencies between (or among) treatment groups, which are commonly included in product applications and reproduced in tabular format in labeling, generally do not take into account the time dependency of adverse events" (FDA 2005, p. 20).

Certain adverse events, e.g., those leading to discontinuation, death, and other serious adverse events, require narrative summaries to be written and submitted. These narratives should not simply repeat in sentence format the information that was presented in the body of the clinical study report in numerical format. Rather, the narratives should permit an adequate understanding of the nature of each adverse event by providing "a complete synthesis of all available clinical data and an informed discussion of the case" (FDA 2005, p. 26). Useful components in a narrative include:

- The participant's age, sex, and treatment group
- Signs and symptoms related to the adverse event being discussed
- An assessment of the relationship of exposure duration to the development of the adverse event
- Concomitant medications, with start dates relative to the adverse event
- Pertinent medical history, physical examination findings, and test results (e.g., laboratory data, ECG data, biopsy data)
- Discussion of the diagnosis as supported by available clinical data (for events without a definite diagnosis a list of possibilities is useful)
- Outcomes and follow-up information

5.2.1 The Utility of Safety Data for Prescribing Physicians and Patients

In addition to enabling regulators to assess the safety of a new drug at the time of its marketing application, and hence to assess the drug's benefit–risk balance in conjunction with efficacy data, a concise summary of the safety data collected during clinical trials is useful to physicians once an approved drug becomes available for prescription. These data provide physicians with the best possible safety data to use when considering, on a case-by-case basis, whether the drug may be a good treatment option for their patients. Similarly, the data also provide patients with information they can consider when discussing treatment options with their physicians.

As Durham and Turner (2008) discussed, when a physician prescribes a new drug for a patient for the first time, both the physician and the patient will be interested in obtaining the best possible answers to several questions, including the following:

- How likely is it that the patient will experience an adverse drug reaction? As will be seen in this chapter, the term adverse event is used in clinical trials to refer to an unwanted event. Since we do not actually know at the time of the event which treatment a clinical trial participant was receiving, the term adverse drug reaction is not suitable. However, once we move into the realm of therapeutic use of a drug, the prescribing physician and the patient will know which drug is being taken, and if an unwanted event occurs, it is now appropriate to use the term adverse drug reaction.

- Are the typical adverse drug reactions temporary or permanent in nature?
- If more than one dose of the drug is available for prescription, how might the risk of an adverse drug reaction vary with each of the doses?
- How might the risk of an adverse drug reaction change with the length of time the drug is taken by a patient? Given that many of today's most prevalent diseases, such as hypertension and diabetes, require long-term pharmacotherapy, this becomes a question of considerable importance.
- Are there identified clinical parameters that should be monitored more closely in a patient once he or she starts taking the drug?
- Is there a possibility that the patient may experience an adverse drug reaction so severe that it is life-threatening? And, if so, what is the likelihood of such an event occurring? A likelihood of 1 in 100 will be viewed very differently by both the physician and the patient than a likelihood of 1 in 1,000,000.

If approved for marketing, safety information collected during clinical trials conducted before the marketing application is made will be summarized in the drug's prescribing information, also known as its package insert. The prescribing information thus provides physicians and patients with the best information available at the time of the drug's marketing approval with which to answer the questions just listed. Generally speaking, the safety evaluation of new drugs is intended to detect quantifiable effects in as many organs and bodily systems as possible, hence the expression "casting a wide net" (Durham and Turner 2008).

5.2.2 Drug Labeling

From a sponsor's perspective, it can reasonably be argued that the driving purpose of all preapproval research and development is to obtain marketing approval supported by the most favorable labeling possible, i.e., labeling that will allow the most widespread prescription of the drug: to obtain the financing to develop additional drugs, biopharmaceutical companies need to sell approved drugs. The content of a new drug's labeling is the result of discussions/negotiations between the sponsor and the regulatory agency considering granting marketing approval. Given regulatory agencies' dual mandate of promoting and protecting public health, regulators wish to allow the drug to be prescribed in all instances where the benefit–risk of doing has a favorable balance while also working to prevent the prescription of the drug to individuals in the target population for whom the benefit–risk balance is not favorable.

Table 5.1 lists the section titles of information presented in a typical label. The "Highlights of Prescribing Information" section comes at the beginning of the label. While it is a useful summary, labels explicitly state that the highlights do not include all of the information needed to use drugs safely and effectively: this more detailed information is provided in the next part of the label, the "Full Prescribing Information."

Table 5.1 Contents of a typical prescription drug's label

Highlights of prescribing information	Full prescribing information
Boxed warning (if any)	Boxed warning (if any)
Recent major changes	Indications and usage
Indications and usage	Dosage and administration
Dosage and administration	Dosage forms and strengths
Dosage forms and strengths	Contraindications
Contraindications	Warnings and precautions
Warnings and precautions	Adverse reactions
Adverse reactions	Drug interactions
Drug interactions	Use in specific populations
	Overdosage
	Description
	Clinical pharmacology
	Nonclinical toxicology
	Clinical studies
	How supplied/storage and handling
	Patient counseling information

5.3 General Safety Descriptions

Safety-related data collected during clinical trials can be considered at three levels: the extent of exposure; common, serious, and other significant adverse events; and common laboratory tests.

5.3.1 Extent of Exposure

The extent of participants' exposure to a drug during a clinical trial is a determinant of the extent to which safety can be assessed from the data collected. Extent of exposure can be characterized in several ways:

- Number of participants exposed
- Duration of exposure
- Dose(s) to which participants were exposed
- Definition of daily dose levels: maximum dose for each participant, dose with the longest exposure for each participant, mean daily dose, and cumulative dose
- Numbers of participants exposed to the dose(s) for certain periods of time
- Profile of exposure for different participant populations: participants broken down by age, sex, ethnic subgroup, disease severity, and concurrent illnesses
- Combined dose–duration: numbers of participants exposed for a given duration to the most common dose or highest recommended dose

5.3.2 Vital Signs

Vital signs typically measured in clinical trials include blood pressure, heart rate, and weight. This is perhaps not surprising since these measures are regarded as general indicators of good health: unwanted increases in blood pressure and heart rate and unwanted increases or decreases in weight can be informative to physicians in clinical practice settings. As well as SBP, diastolic blood pressure (DBP) is typically measured. Heart rate is sometimes legitimately referred to as pulse rate: medical examinations in a physician's office typically evaluate heart rate by palpating pulses in arteries in the wrist. For continuous data, such as blood pressure, heart rate, and weight, descriptive data providing information about central tendency and dispersion are useful.

Categorical data can also be informative, and the associated categories can take various forms. Consider the following example provided by Durham and Turner (2008). Imagine a clinical trial in which the treatment phase lasts 12 weeks. Vital signs (and multiple other parameters) are assessed at baseline and then every 2 weeks throughout the treatment period: there will therefore be a baseline value for each participant and six time points at which the participants' vital signs may have deviated from their baseline values. It may be of interest to the study team to know how many participants showed clinically significant changes in vital signs throughout the trial. Since the definition of a clinically significant change requires a clinical judgment to be made, clinicians on the study team would need to define what they considered to be clinically significant changes at the time of the trial's design, and this information would need to have been included in the trial's statistical analysis plan. The following changes in blood pressure and heart rate are illustrative hypothetical examples of what might be examined at each of the six time points during the trial:

- An increase from baseline in SBP $\geq$ 20 mmHg
- An increase from baseline in DBP $\geq$ 12 mmHg
- An increase from baseline in heart rate $\geq$ 15 beats per minute (bpm)

In addition to focusing on one time point at a time when looking for changes of predefined magnitudes, it may also be of interest to the study team to investigate the possible occurrence of sustained changes across time. Hypothetical examples might be:

- An increase from baseline in SBP $\geq$ 15 mmHg at each of three consecutive visits
- An increase from baseline in DBP $\geq$ 10 mmHg at each of three consecutive visits
- An increase from baseline in heart rate $\geq$10 bpm at each of three consecutive visits

In these carefully constructed hypothetical examples, the magnitudes of change from baseline that are of interest when looking at three consecutive time points are smaller than those when looking at the changes one time point at a time. These

magnitudes were chosen simply to raise the possibility that a smaller change that is maintained over a period of time may be more of concern than a larger change that is identified on just one occasion.

5.3.3 Adverse Events

The varying nomenclature used to describe safety data in clinical trials can be confusing. Terms used include adverse events, adverse experiences, adverse drug reactions, side effects, severe adverse events, significant adverse events, treatment-emergent adverse events, adverse events of special interest, and toxicities. We therefore endeavor to bring some consistency to this terminology.

When reporting the results of a clinical trial, it is of interest to know about the frequency of all adverse events that occurred and any relationships with time, demographic characteristics, and relation to drug dose or concentration. It is also of interest to differentiate as much as possible between those adverse events that are drug related, i.e., those where there is a reasonable possibility of a relationship to the drug administered and those that are not. During the course of a clinical trial, it is likely that most participants will have some form of adverse events: the longer the trial and the sicker the participants, the more adverse events there will be. Since adverse events do not actually have to be related to the treatment, the sites report "everything from colds, to falls, to car accidents, to murder, as well as all the typical medical conditions that might be monitored by any doctor" (Prokscha 2007). Adverse events can be grouped into various categories. Open adverse event reports capture the event in the participant's own words or in the investigator's version of the participant's words. Another category is adverse events of special interest. When previous trials in a drug's development program have shown a history of certain kinds of adverse events, there may be particular interest in the frequency and severity of these specific adverse events during the course of the study. A list of these signs/symptoms is provided, and both participants and investigators look for these events. For events in both categories, the investigator generally makes an assessment of severity, relationship to the treatment, action taken, and start and stop dates (or the start date along with a note that the event is ongoing).

5.3.4 Common Laboratory Tests

There is a wide range of clinical chemistry tests that can be conducted. For example, liver function tests include ALP (alkaline phosphatase), ALT/SGPT (serum glutamic pyruvate transaminase), AST/SGOT (serum glutamic oxaloacetic transaminase), albumin, bilirubin, globulin, LDH (lactic acid dehydrogenase), and total protein. Renal function tests include BUN (blood–urea–nitrogen), creatinine, and creatinine clearance.

Most therapeutic confirmatory trials are run at multiple investigative sites to facilitate enrollment of sufficient participants. In most cases, samples from all of the investigative sites in a clinical trial are shipped to a central laboratory. Analysis of data that have been collected from many sources and then pooled into one data set can lead to considerable statistical problems. Since the majority of laboratory measurements are surrogates and reference ranges can vary from analytical method to method, many different types of errors can occur during laboratory testing. These can be due to variation in many aspects of data collection, including the technician, an instrument, the environment, and the reagents used. While statistical approaches to standardize values from several local laboratories, each with their own reference ranges, have been described (Chuang-Stein 1992), central laboratories provide a real statistical advantage in this context. All samples are analyzed in the same manner in the same laboratory, thereby providing a much better data set. As Chow and Liu (2004) noted, "laboratory data obtained from central laboratories are more accurate and reliable compared with those obtained from local laboratories."

5.3.5 Examples of Safety Tables Included in Clinical Study Reports

In contrast to analysis methodologies for efficacy data, the analysis of general safety data in clinical trials is not rigorously defined. Chow and Liu (2004) commented on the problems in defining, capturing, and evaluating safety-related data and also noted that both FDA and ICH guidelines state that every adverse event need not be subjected to rigorous statistical evaluation. As a result, "the analysis of adverse events is basically descriptive in nature" (Chow and Liu 2004). Descriptive statistics for adverse events obtained from clinical trials typically include rates of occurrence of adverse events in exposed groups overall and also among defined groups of participants (e.g., according to age and sex) to look for differential rates of adverse events.

Comparing rates of adverse events between two groups may seem a straightforward and reasonable strategy. However, such a comparison is only reasonable if the length of observation (i.e., time at risk) is equal between the groups. O'Neill (1987) proposed alternative methods of presenting adverse event data that take into account varying times at risk. Such approaches can shed light on the time course of the adverse events.

Several summary tables are commonly presented to report safety data. Two examples of typical formats are provided here. Table 5.2 shows the format for the overall summary of adverse events falling within several adverse event categories. It is actually a table shell that is prepared by medical writers in advance of the study's results being available: preparation in advance of the availability of the data saves time during the preparation of the clinical study report once the data are available.

Table 5.3 shows the table shell for the summary of the most common adverse events. The precise meaning of the phrase most common must be defined every time it is used. In this example it is defined by the statement "Greater or equal to 10 % in

Table 5.2 Overall summary presenting number and percentage of participants experiencing adverse events (trial ABC123)

Adverse events (AEs)	Number (%) of participants	
	Drug ($N=1,500$)	Placebo ($N=1,500$)
Pretreatment AEs	xx (xx)	xx (xx)
On-treatment AEs[a]	xx (xx)	xx (xx)
Drug-related AEs[b]	xx (xx)	xx (xx)
Serious AEs	xx (xx)	xx (xx)
AEs leading to withdrawal	xx (xx)	xx (xx)

[a]AEs that occur on any treatment, active or nonactive
[b]"Drug-related" is a designation made by an investigator when deciding that there is a reasonable chance that the AE was caused by the treatment being taken

Table 5.3 Number and percentage of participants experiencing the most common (≥10% in either treatment group) adverse events (trial ABC123)

Adverse event	Number (%) of participants	
	Drug ($N=1,500$)	Placebo ($N=1,500$)
Any event	xx (xx)	xx (xx)
Event A	xx (xx)	xx (xx)
Event B	xx (xx)	xx (xx)
Event C	xx (xx)	xx (xx)
Event D	xx (xx)	xx (xx)
Event E	xx (xx)	xx (xx)

either treatment group." Note that it is possible (indeed very likely) that the incidence of side effects will not be identical in the two treatment groups. Some adverse events that occur in more than 10% in the drug treatment group may occur in less than 10% in the placebo treatment group and vice versa. Data for both treatment groups employed will be provided for any adverse event listed for either group. Data are often presented in descending order of occurrence. Possibilities for adverse events making a most common list include headache, insomnia, nausea, fatigue, and dizziness.

5.3.6 Shift Analysis

Shift analysis is a statistical approach in which the data described are not the actual numeric values of the laboratory tests themselves (e.g., hemoglobin levels), but what is termed a categorical ordinal variable. Categorical variables include sex: a person is either a male or a female. In this case there is no order associated with the categorization. In contrast, a given laboratory value may fall within a reference range (a range of values designated as representing normal values), below that reference range (hence being termed low), or above the reference range (hence being termed high). The designations low, normal, or high mean that, in this case, an order is associated with a variable's placement into one of the categories.

Table 5.4 Shift analysis of hemoglobin values

	Baseline value					
	Placebo treatment group ($n=20$)			Drug treatment group ($n=20$)		
Last visit value	Low	Normal	High	Low	Normal	High
Low	3 (15 %)	5 (25 %)	0	1 (5 %)	4 (20 %)	1 (5 %)
Normal	2 (10 %)	7 (35 %)	2 (10 %)	1 (5 %)	11 (55 %)	0
High	0	1 (5 %)	0	0	0	2 (10 %)

Reproduced with permission from Durham and Turner (2008)

By placing participants' laboratory values at the beginning of a trial (baseline values) into one category and their values at future points in time (perhaps one-quarter, one-half, and three-quarters of the way through their participation in the trial and also at the end of the trial), it is possible to determine the proportion of individuals who shifted from one category to another. Depending on the nature of the specific laboratory test, a shift from normal to high may be of concern, as might a shift from normal to low. Shifts from low to high or high to low may also be of interest (Durham and Turner 2008).

A typical summary table presenting the results of this kind of analysis is presented as Table 5.4. For example, the table shows that 25 % of the participants in the placebo treatment group who had normal hemoglobin values at baseline had low values at the end of the trial: for the drug treatment group, this value was 20 %. The relative importance of this difference would then be assessed by the study team.

5.3.7 Responders' Analysis

As we have already noted, no biologically active drug is free from the possibility of adverse events occurring in genetically and/or environmentally susceptible individuals. In some cases, a certain small degree of change in a laboratory parameter may be acceptable as long as appropriate therapeutic benefit is conferred by the drug. However, a question of interest then becomes as follows: What is the likelihood that a given patient may experience a degree of change that is not considered acceptable?

An analysis approach that may be informative in this case is one in which a change from baseline to the end of the trial is calculated for each participant and the changes from baseline are used to categorize each participant as either a non-adverse responder (an individual whose change from baseline was within the acceptable range of change) or an adverse responder (an individual whose change from baseline was greater than the acceptable range of change). The descriptive analysis in this scenario includes the presentation of counts and percentages of each kind of responder in each treatment group.

Extending this basic approach, data may be presented for multiple time points within the individual's overall participation in the trial (perhaps one-quarter, one-half, and three-quarters of the way through participation) as well as at the end of the individual's participation in the trial. A second line of extension is to place the changes

from baseline into more than two categories. An example of this would be to determine the numbers of individuals who showed an acceptable degree of change, a degree of change that is a certain magnitude above the acceptable degree of change, and a degree of change that is a greater magnitude above the acceptable degree of change.

5.4 A Key Reason for the Nature of General Safety Descriptions

As noted at the beginning of this chapter, general safety assessments employ descriptive statistical approaches as opposed to the hypothesis-testing approach that is used when assessing efficacy. We saw in Chap. 4 how appropriate statistical care needs to be taken when conducting multiple hypothesis testing in the efficacy realm. If we now consider the enormous amount of general safety data collected in a clinical trial, adopting the same strategy for multiplicity corrections would be cumbersome and, even if performed, likely non-informative. To have any reasonable chance of attaining statistical significance, an enormously larger number of trial participants would be needed.

General safety analyses may therefore be regarded as hypothesis generating more so than hypothesis testing. If the same adverse event is seen in an unanticipated manner in several trials within a drug's clinical development program, it may be reasonable to consider that the drug is truly giving rise to this pattern of adverse events. In this case, it would therefore be reasonable to regard this occurrence as a safety signal deserving of further investigation. A new trial could then explicitly focus on this adverse event and employ hypothesis testing to determine if the safety signal is indeed alerting us to a real phenomenon.

5.5 The Intersection–Union and Union–Intersection Tests

In the domain of proarrhythmic cardiac safety, QT prolongation can be regarded as an adverse event of special interest, and therefore an inferential (hypothesis-testing) statistical approach is taken. Three statistical methodologies are applicable here: the first two, the intersection–union test and the union–intersection test, are discussed in this section; concentration–response modeling is then discussed in the following section.

5.5.1 The Thorough QT/QTc Study

The Thorough QT/QTc (TQT) Study is addressed by ICH Guideline E14 (ICH 2005). It is discussed in more detail in Chap. 7, but a brief description here is appropriate to facilitate discussion of the role of the intersection–union test in this context.

The TQT study's purpose is to prospectively exclude an unacceptable degree of drug-induced QT interval prolongation. The name of the study results from two considerations. First, while rigorous experimental methodology is essential in all clinical research, all aspects of this study are conducted under particularly tightly controlled conditions. The decision criteria are strict, and the QT interval is measured intensively over a wide time interval. These considerations lead to the term "Thorough." Second, while it is the QT interval that is measured, it is a subsequently computed value called QTc that is analyzed, where "c" stands for "corrected for heart rate." The QT interval varies to a certain degree with heart rate in an (imperfect) inverse manner: as heart rate gets faster, the QT interval gets shorter. It is therefore considered appropriate to correct the measured QT interval for heart rate.

The traditional TQT study has four treatment arms:

- A positive control arm, comprising of a drug that is known to increase the QT interval by around 5 ms. It is necessary to establish assay sensitivity, i.e., to demonstrate that the methodology employed is able to detect a prolongation of the QT interval when it is indeed present.
- A placebo arm, against which the drug is compared.
- The proposed therapeutic dose of the drug.
- A supratherapeutic dose of the drug: unless the proposed dose is close to the maximum tolerated dose, the supratherapeutic dose is likely to be several multiples of the proposed dose.

With regard to the positive control arm, it may initially seem paradoxical that a drug that is known to prolong the QT interval is given to TQT study participants. Given that the purpose of the field of proarrhythmic cardiac safety revolves around the potential torsadogenic liability of such increases, it is perfectly reasonable to ask why the administration of such a drug would be involved. The answer is that an increase of 5 ms has been determined to have an extremely small likelihood of causing ventricular arrhythmias of clinical concern. Therefore, the benefits of administering a positive control that leads to a 5 ms increase, i.e., the ability to determine the true QT liability of the drug, are considered to outweigh the risks of its administration. Additionally, should a study participant experience any form of ventricular arrhythmia of clinical concern, the fact that TQT studies are conducted in residential clinical pharmacology units means that the person would have immediate access to appropriate medical care of the highest quality by physicians who are extremely skilled in addressing this occurrence. The antibacterial agent moxifloxacin is commonly, but not exclusively, employed in this context.

The supratherapeutic dose treatment arm is intended to mimic the "worst-case scenario" in which higher-than-intended concentrations may result, e.g., in certain patients with hepatic or renal impairment and resultant metabolic or excretion blockade, from accumulation, or from drug–drug interactions with concomitant medications.

TQT studies are typically conducted at some point following completion of single- and multiple-ascending dose (SAD and MAD) and maximum tolerable dose

(MTD) studies, which help determine the safest supratherapeutic dose (frequently the most difficult choice in TQT study designs). Further, optimal TQT study design requires fundamental knowledge of the drug's clinical pharmacokinetic profile, including estimates of C_{max} and T_{max}, since QT prolongation must be assessed shortly before, at, and shortly after T_{max} in addition to some later time points: these typically include 24 h after drug administration and additional later time points should the drug have late-appearing metabolites that may themselves have a proarrhythmic influence. On the order of 10–15 time points may be utilized for measurement of QT effects.

The regulatory threshold of concern for drug-induced QT interval prolongation of regulatory concern as described in ICH E14 is "around" 5 ms (ICH 2005), which is statistically operationalized by placing the upper bound of a one-sided 95 % confidence interval on the mean difference point estimate (drug minus placebo) for each time point: this is done for both the therapeutic and supratherapeutic doses. If no upper bounds breach the noninferiority margin of 10 ms, the study is termed "negative," and no further regulatory scrutiny falls on the drug. If any upper bound breaches the noninferiority margin, the study is termed "positive." In this case, more extensive and intensive ECG/QT evaluations will be required during the rest of the drug's development than would usually occur for a drug in its class.

5.5.1.1 Establishing Assay Sensitivity

Hypothesis testing is conducted to establish assay sensitivity. Assay sensitivity is demonstrated by rejection of the null hypothesis in favor of the research hypothesis. Assay sensitivity is tested by placing the lower bound of a one-sided 95 % confidence interval on the treatment effect point estimate (calculated as moxifloxacin minus placebo) for each time point. In this context, therefore, the null hypothesis is the intersection of several hypotheses, i.e., that the lower bound of the one-sided 95 % confidence interval is $\leq$5 ms for all specified time points. Rejection of the null hypothesis occurs if the lower bound of the one-sided confidence interval for any of the measurement times is above 5 ms, i.e., a union of the rejection regions for each of the individual times. Thus, the nature of the two hypotheses leads to the name union–intersection test. This result indicates that there is compelling statistical evidence that the experimental methodology will be able to detect QT/QTc prolongation induced by the drug if it truly exists (based on the 5 ms threshold).

5.5.1.2 Evaluating the Therapeutic and Supratherapeutic Doses of the Drug

Once assay sensitivity has been established, the data for the therapeutic dose and supratherapeutic treatment arms can be analyzed and interpreted. The same statistical analysis is used for each dose separately. As previously noted, the drug's QT prolonging effect is tested by placing the upper bound of a one-sided 95 %

confidence interval on the treatment effect point estimate (calculated as drug minus placebo) for each time point. Here, the null hypothesis is the union of several hypotheses, i.e., that the upper bound of the one-sided 95 % confidence interval is ≥10 ms for at least one of the time points studied. The research hypothesis (also known as the alternative hypothesis) is the intersection of several hypotheses, i.e., that the upper bound of the one-sided 95 % confidence interval is <10 ms for all time points studied and the intersection of all of these one-sided tests. If any one of the upper bounds is equal to or exceeds 10 ms, the null hypothesis would fail to be rejected and the study would be considered positive for QTc prolongation. If all of the upper bounds are less than 10 ms, the null hypothesis would be rejected in favor of the research hypothesis and the study would be considered negative for QTc prolongation, provided that assay sensitivity had first been established.

5.5.1.3 Control of Multiplicity Issues in Thorough QT/QTc Trials

Imagine a TQT study in which QT interval measurements will be made at 12 time points, and consider first the evaluation of the establishment of assay sensitivity. As QTc effects are evaluated at each time point, there are 12 opportunities for the lower bound of the one-sided 95 % confidence interval placed around the treatment effect to exceed 5 ms. The more time points that are included in the study's design, the greater the chance of establishing assay sensitivity by chance alone, i.e., the greater the probability of falsely establishing assay sensitivity. Therefore, the test of the null hypothesis (equivalently, the confidence intervals associated with each assessment time) needs to make use of a multiple testing procedure that maintains a one-sided type I error of 5 % overall. Hence, the assay sensitivity testing must employ an appropriate multiple testing procedure, such as Hochberg's, if multiple hypotheses or times are being tested (Zhang and Machado 2008).

Consider next the evaluation of the therapeutic dose. In this hypothetical example utilizing 12 time points, there are 12 opportunities for the upper bound of the one-sided 95 % confidence interval placed around the treatment effect to exceed 10 ms. The more time points that are included in the study's design, the greater the chance of finding an instance of a magnitude of QTc prolongation of regulatory concern by chance alone, i.e., the greater the probability of falsely identifying the drug's QT prolongation liability as being of regulatory concern. Statistical adjustment for these multiple comparisons is completed through the powering of the trial for two reasons: the type I error rate for the assessment of QTc prolongation is specified in ICH E14 at 5 % (one sided), and the roles of type I and type II errors are switched through placing the burden of proof for no QTc prolongation on the sponsor. The sponsor may choose to power the study for testing either the supratherapeutic dose alone or, more cautiously, for both dose levels.

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Chapter 6

Meta-analysis, Group Sequential Study Designs, Centralized Endpoint Adjudication, and Composite Endpoints

The analytical methodologies introduced in this chapter can be employed in the analysis of efficacy and safety data: our interest lies with their use in the domain of cardiovascular safety.

6.1 Introduction

This chapter introduces four analytical methodologies that can be used to analyze efficacy or safety data. Each is described in turn, and our interest then focuses on their employment in the domain of cardiovascular safety.

Meta-analysis is a statistical technique that brings together data from multiple studies addressing the same topic, thereby employing a (potentially much) larger database to answer a research question than was possible on the basis of data from each of the individual studies. Meta-analysis is useful in both clinical research and clinical practice. In the realm of clinical practice, physicians need to be familiar with the most recent and relevant research published in the medical literature to enable them to practice evidence-based medicine. While research reports of individual randomized clinical trials are helpful to physicians, it has become very difficult (and arguably impossible) for them to read every publication of relevance to their particular specialty. Two types of approaches that bring together the results from multiple studies into a single publication have therefore attracted increasing attention. The first is qualitative in nature, while the second is quantitative. Systematic reviews are descriptive in nature: they "collate, compare, discuss, and summarize the current results" in a particular field (Matthews 2006). Meta-analysis goes a step further, providing a statistical technique to combine results from multiple individual trials and then to use this data set to conduct a new analysis that could not be conducted on the basis of any of the individual trial's data sets.

Group sequential designs facilitate interim analyses. As the name connotes, these analyses are performed during the conduct of a study, i.e., before the study has gone to the full term as outlined in its study protocol. Several interim analyses may be performed during an ongoing clinical trial at various pre-identified points. Each interim analysis conducted utilizes all of the data that have been collected to the point when a

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given analysis is conducted. This analytical approach has the strength that it may reveal compelling evidence that the clinical trial should be stopped (terminated) at the time of a particular interim analysis because there is already compelling evidence that the drug is effective, that it is toxic, or that, even if the trial were to carry on to its conclusion, there would very likely still not be compelling evidence of efficacy or toxicity.

The size and hence geographical distribution of investigational sites needed for the large cardiovascular safety outcome trials discussed in Chap. 13 mean that there can be a considerable degree of variability in the "identification" of cardiovascular endpoints of interest since classification of events as "actual" study endpoints is a partially subjective process based on the application of a complex set of medical endpoint criteria to an often complex clinical event. Regulatory agencies therefore require the centralized adjudication of these events to control for the impact of this variability in "identification" and thereby to generate data for use in statistical analyses that are as standardized as possible.

Composite endpoints are used in these cardiovascular outcome safety trials since the occurrence of individual events is typically low. The statistical rationale for employment of these endpoints is explained.

6.2 Meta-analysis

The underlying logic behind meta-analysis is straightforward: by creating a larger data set than existed for any of the individual trials included, increased power is provided to detect statistically significant treatment effects and to facilitate assessment of the magnitude of a treatment effect more precisely. For many reasons, there are likely to be more than one clinical trial that has addressed the same research question: combination of information from multiple smaller studies that are inconclusive sometimes paints a picture that is more compelling.

6.2.1 More Informative Nomenclature: The Term Meta-methodology

While the term meta-analysis is now well embedded in the medical literature, the term meta-methodology represents more informative nomenclature (Turner and Durham 2014). The name meta-analysis is typically used in the literature to refer to the entire process of conducting such an analysis: however, it does not adequately capture and emphasize the need for methodological rigor in the full array of actions required. Certainly, an analysis is conducted, and the term meta-analysis is entirely appropriate when discussing that segment of the process. However, determining the individual data sets from which the new data set is created, choosing the appropriate analytical model, and presenting the statistical results of the meta-analysis and their interpretation with scientific and clinical decorum are also critically important.

6.3 The Fundamentals of Meta-methodology

Meta-methodology facilitates a quantitative evaluation of the combined evidence provided by two or more individual clinical trials that have addressed the same research question (Turner and Durham 2014). Most frequently, it involves the statistical combination of summary statistics from each trial included in the analysis, i.e., mean treatment effect point estimates and the variances associated with those estimates. In these cases, study-level data are employed in the analysis. However, it can also involve analyses performed using the raw data from each participant in each trial contributing to the new data set. In such cases, the meta-analysis is said to be performed on participant-level data. While the latter is always preferable if possible, it can be challenging to access such data for a variety of reasons, including availability of participant-level data due to their proprietary nature and, in some cases, obtaining approval from an institutional review board.

The fundamental steps in study-level meta-methodology include the following (Turner and Durham 2014):

1. Establishing rules for determining whether or not the data from an identified study report of potential relevance will be incorporated into the new data set
2. Identification of all potentially relevant studies
3. Data extraction, i.e., obtaining the treatment effect point estimate and its variance for each study to be included in the analysis
4. Data analysis, i.e., conduct of the meta-analysis itself
5. A visual inspection and quantitative test of homogeneity
6. Evaluation of the robustness of the result obtained from the meta-analysis
7. Dissemination of results, interpretations, and conclusions at scientific conferences and in medical and scientific publications

6.3.1 Determining the Studies to Be Included

One straightforward approach is to decide to include every study that can be identified, whether identified from a literature search or other routes. A counterargument to this approach, however, is that some of the studies that will be identified will almost certainly be "better" than others and that "less good" studies should perhaps not be included. In the latter case, strict a priori inclusion and exclusion criteria that operationally define entry into the analysis must be stated by the researchers conducting the meta-methodological investigation in advance of searching for studies. In this sense, while no data are being collected in a new clinical trial, it is highly advisable to write a "meta-methodology protocol" before executing a meta-methodology in exactly the same way that a study protocol is written ahead of conducting a new trial.

6.3.2 Identification of all Potentially Relevant Studies

Identification of all studies in the published medical and scientific literature that may potentially be included has become much easier with the advent of computer search engines and web-based tools, but it can still be a challenging task. One particular difficulty is looking for, and, when located, obtaining unpublished data. The issue of publication bias is a particularly noteworthy one in this context (Turner and Durham 2009). Piantadosi (2005, pp 582–3) defined publication bias as a "tendency for studies with positive results, namely those finding significant differences, to be published in journals in preference to those with negative findings." In a similar vein, Steward and colleagues (2005, p 262) commented as follows:

> Overt or subconscious pressures such as the wish to bolster research ratings, the need to sell journals or simply the desire to deliver good news can lead to results being presented in an over-favourable light, or to publishing only a message of progress of progress or improvement. This is of course potentially very damaging, and in the context of systematic review it is important that we do all we can to minimize sources of potential bias, including those associated with publication and reporting.

Additional factors of relevance here are that studies with positive results are more likely to be published in English language journals, and hence located more readily by some large computer search engines, and that some studies are never submitted for publication since those conducting the study determine subjectively that the results are unfavorable; however, "unfavorable" is operationally defined by the researchers. This means that it is very important for researchers conducting a meta-analysis (meta-analysts) to do everything possible to locate any unpublished study results. As Kay (2007) wryly observed, "to ensure that a meta-analysis is scientifically valid, it is necessary to plan and conduct the analysis in an appropriate way. It is not sufficient to retrospectively go to a bunch of studies that you like the look of and stick them together!"

6.3.3 Data Extraction and Acquisition

When conducting a study-level meta-analysis, this step is straightforward: two items of data are acquired from each study report:

- A measure of the treatment effect in that study, represented by the treatment effect point estimate presented in the report
- The variance associated with the treatment effect, often operationalized as a two-sided 95 % confidence interval placed around the treatment effect point estimate

6.3.4 Executing the Actual Meta-analysis

Meta-analysts must decide before conducting the analysis whether to employ a fixed-effects or a random-effects analysis model. These differ in the degree of influence each individual study's treatment effect is allowed to exert mathematically on the new treatment effect point estimate calculated by the meta-analysis: this degree of influence is operationalized by the weight assigned to each treatment effect.

Each study included in the analysis contributes the same two pieces of information: the treatment effect point estimate found in that study and its associated variance. Therefore, if the analysis incorporates 100 studies, 100 treatment effect point estimates are included. However, each item of information does not necessarily impart the same influence (in statistical nomenclature, does not carry the same weight) when determining the result of the analysis: studies whose treatment effect point estimates are weighted more heavily will exert a greater influence on the final result of the analysis than those whose treatment effects are weighted less heavily. The weight accorded to each study-specific treatment effect is determined computationally according to the rules of the analysis model adopted. Both the fixed-effects model and the random-effects analysis model use the precision of each study's treatment effect point estimate when assigning its weight: higher precision, conveyed by narrower confidence intervals around the treatment effect point estimate, affords more weight. However, and very importantly, when determining the weight assigned to each study's treatment effect point estimate, the random-effects model also uses an estimate of how different from each other the studies are in various characteristics, such as the nature of the study population, number of participants in each treatment group, length of treatment periods, participants' concomitant illnesses, and the quality of measurements made during the trial. In cases where the natures of the studies are very similar, the difference in the results generated by the two analysis models would be small: if there were no differences at all, the results would be the same. However, the greater the degree of difference between the studies incorporated in the analysis, the greater the difference between the results generated by the two models, and the more important it becomes to employ the random-effects model in situations where the studies included in the meta-analysis do indeed differ from each other.

Allowing for the existence of differences between studies included in the meta-analysis is an intuitively sensible feature of the random-effects model, since in most circumstances when comparing multiple studies conducted by multiple independent research teams, it would be very surprising if the studies incorporated did not vary from each other. While the precise methods of quantitatively estimating the differences between studies (i.e., the additional component of the determination of the weight assigned to each study's treatment effect point estimate in addition to its precision) need not be discussed here, it is important to be aware of the consequences of employing a fixed-effects model when a random-effects model is the

more appropriate choice. The random-effects model tends to generate wider confidence intervals around the newly created treatment effect point estimate, indicating less precision. If a fixed-effects model is employed when there are considerable differences between the studies included, the confidence interval will be narrower than it would have been had the random-effects model been used, and thus the confidence placed in the result of the analysis will be greater than it should be. Narrower confidence intervals also make it easier to achieve a statistically significant result, an outcome used by some meta-analysts to ascribe more gravitas to their results than they deserve: consideration of a result's clinical significance is more important, and the clinical assessment of a treatment effect is "a completely separate assessment" from its statistical significance (Durham and Turner 2008).

An illuminating example can be found in a paper by DiNicolantonio and colleagues reporting a study-level analysis comparing the beta-blocker carvedilol with four β-1 selective beta-blockers (DiNicolantonio et al. 2013). As part of the overall meta-methodological approach, three trials including 644 participants with acute myocardial ischemia and evaluating relative reductions in all-cause mortality were combined for meta-analysis. Of particular interest here is that the authors reported results using both a fixed-effects model and a random-effects model. For the fixed-effects model, the result was as follows:

$$\text{Relative risk ratio} = 0.55\left(95\%\,\text{CI}: 0.32 - 0.94,\ p = 0.03\right)$$

Of note is that both the lower and the upper limits of the confidence interval lie below zero. This result can therefore be interpreted in this manner:

> The result from this meta-analysis indicates a statistically significant reduction in all-cause mortality associated with carvedilol in the general population. The result is compatible with a reduction as great as 68 % and as small as 6 %, and our best estimate is a reduction of 45 %.

The result for the random-effects model was as follows:

$$\text{Relative risk ratio} = 0.56\left(95\%\,\text{CI}: 0.26 - 1.12,\ p = 0.10\right)$$

Of note in this case is that the lower and the upper limits of the confidence interval span zero. For this model, the result is therefore interpreted in this manner:

> The result from this meta-analysis does not indicate a statistically significant reduction in all-cause mortality associated with carvedilol in the general population. The result is compatible with a reduction as great as 74 % but also compatible with an increase as great as 12 %. Our best estimate is a reduction of 44 %.

The important point made by this example is that the best estimates of the truth in the general population provided by the fixed-effects and random-effects models are essentially the same (relative reductions in all-cause mortality of 45 and 44 %), but the statements of the statistical significance of the results are completely different due to the widths of the respective confidence intervals. For the fixed-effects model, the lower and upper limits of the confidence interval (0.32 and 0.94,

respectively) both fall below 1.0, hence the attainment of statistical significance. For the random-effects model, the lower and upper limits (0.26 and 1.12, respectively) of this wider confidence interval lie on either side of 1.0, hence the failure to attain statistical significance. The authors are to be commended for presenting the results generated by both analysis models.

6.3.5 Testing for Homogeneity

The statistical theory underpinning meta-analysis assumes that the study-specific estimates of the treatment effect are (relatively) homogenous. Homogeneity is present when the study-specific estimates are similar in magnitude and direction to the estimate of the treatment effect resulting from the combined analysis. Heterogeneity can arise from differences between studies, such as the possibilities noted in the previous section. Since the objective is to calculate a well-justified combined estimate of the treatment effect of interest, a formal evaluation of homogeneity following a visual graphic inspection of the combined effect against each individual effect is a recommended strategy.

This formal evaluation involves a statistical test, such as the Cochran Q test. Homogeneity (also expressed as lack of heterogeneity) is indicated by a statistically nonsignificant result. While general acceptance of the $\alpha = 0.05$ criterion provides a "line in the sand" that is useful in certain circumstances, blind adherence to characterizing a result as either statistically significant or not statistically significant using the $\alpha = 0.05$ level is not necessarily a clinically meaningful strategy. In this context, a statistically nonsignificant Cochran test can be (mis) interpreted to state that there is no heterogeneity present. That is, a fallacious argument can be made that the lack of statistically significant evidence of heterogeneity represents an all-or-none statement of its complete absence.

6.3.6 Evaluating Robustness

Having calculated the result of the analysis, it can be informative to assess its robustness. In any combined analysis, some of the studies included will be larger than others, and sometimes a small percentage of included studies can be considerably larger than the majority of others. The nature of the calculations performed here mean that the larger trials tend to influence the result more, since they tend to have greater precision.

It can therefore be helpful to assess the robustness of the overall conclusion by performing the analysis without the data from the largest study or studies to see if the results remain qualitatively the same. If they do, then the result of the primary overall analysis is deemed robust. If they do not, confidence in the overall result can be undermined. Moreover, if the results are considerably different, it simply may not be appropriate to present the combined result alone and make statements based on it.

6.3.7 Disseminating the Results, Interpretations, and Conclusions to Various Audiences

The results presented upon completion of the meta-analysis would typically include the following:

- The treatment effect point estimate for each individual study included in the analysis and the confidence interval (often the two-sided 95 % CI) placed about each study's estimate
- The overall treatment effect point estimate calculated in the meta-analysis and its confidence interval (often a two-sided 95 % CI)

This information can be displayed in tabular form or in a graphical form called a confidence interval plot.

6.3.8 Additional Challenges in Meta-methodology

Meta-methodology has both strengths and weaknesses. As Turner and Durham (2009, p 254) commented:

> As is true across all research methodology, if the correct study design has been employed and rigorous methodology has permitted the acquisition of optimum-quality data, the computational analysis is typically not difficult. What is more difficult is the interpretation of the results and the appropriate degree of restraint needed to disseminate one's conclusions in a responsible manner. Given all of these considerations, the conduct and communication of a meta-analysis must be undertaken carefully, diligently, and responsibly.

The computational analysis in meta-methodology is not difficult. The maturity and intellectual honesty of the meta-analysts lies in the choice of studies to be included in the analysis, the choice of the appropriate analysis model, the interpretation of the results, and the appropriate degree of restraint needed to disseminate their conclusions in a responsible manner in the best interests of both individual patients and public health. Perhaps more than for any other statistical analysis commonly reported in the scientific and medical literature, interpretations and conclusions can be alarmingly subjective: a case study presented in Chap. 12 exemplifies this occurrence.

6.3.9 A Potential FDA Guidance for Industry

In November 2013, the FDA held a public meeting entitled "Meta-Analysis of Randomized Controlled Clinical Trials for Safety Evaluation," the agenda for which is available on their web site (FDA 2013a). They also released an associated white paper on the topic as a means to generate discussions (FDA 2013b). The paper commenced as follows:

> This document covers a range of topics on the appropriate use of meta-analysis of randomized controlled clinical trials (RCTs) to evaluate the safety of pharmaceutical products in the context of regulatory decision-making. Comments received from the public on this document will be considered in developing FDA guidance for applicants submitting new drug applications (NDAs), biologics licensing applications (BLAs), or supplemental applications on the appropriate use of meta-analyses of RCTs for safety evaluation. The planned guidance is also intended for FDA reviewers and for third-party entities that prepare or evaluate meta-analyses assessing the safety of regulated products, as there is currently no FDA guidance on how to evaluate the quality and persuasiveness of meta-analysis for regulatory decision-making. Specifically, this guidance will describe our view of various aspects of the evidentiary criteria considered important by FDA when evaluating the strength and quality of evidence provided by a meta-analysis.

As of writing this text, the guidance document is still in the development process.

6.4 Group Sequential Designs

Group sequential designs facilitate interim analyses being performed during the conduct of a clinical trial. Each interim analysis that is performed utilizes all of the data that have been collected to the point when a given analysis is conducted.

Before moving to the more detailed discussion that follows, it is important to emphasize that the word "group" in the name group sequential design is used differently from the situations that have been described previously. In this case it does not refer to a treatment group, i.e., a group of participants receiving one of the multiple treatments employed in the trial (e.g., the drug treatment group rather than the placebo treatment group). Rather, it refers to the fact that a group of participants (comprising of participants from both treatment groups) completes their participation in the study before the initial interim analysis is conducted, a second group of the same number of combined participants completes their participation before the second interim analysis is performed, and so on. An assumption when employing this methodology is that fairly close to equal enrollment has occurred in each treatment group at each point at which an interim analysis is conducted.

6.4.1 Interim Analyses in Group Sequential Trials

The purpose of interim analyses in group sequential trials is to determine if the clinical trial should be terminated at that point. The rationale for interim analyses of data that are accumulating over time in a clinical trial was established several decades ago, and considerable attention has subsequently focused on the development of statistical approaches and decision-making processes that facilitate the implementation of data monitoring and interim analyses for the early termination of a clinical trial (Chow and Liu 2004).

One reason for the early termination of a clinical trial in which the primary focus was an investigation of the drug's efficacy would be that the interim analysis provided compelling evidence that the drug under investigation was indeed effective. From an ethical standpoint, this would mean that, if the trial were continued, participants randomized to the placebo treatment group would be receiving a treatment that was then known to be inferior to the drug, and hence there is no ethically justifiable reason to continue the trial. While the ethical considerations are paramount, there are also other benefits to termination in this scenario. From an economic standpoint, a sponsor would save the cost of continuing with the clinical trial, allowing the saved resources to be redirected to the development of another compound, and, from a public health perspective, the drug could be approved for marketing earlier, thereby being available to clinicians and patients at an earlier time.

A second reason for stopping the trial would be that there is compelling evidence that the trial will not be able to achieve its intended purpose even if it carries on to its maximum number of participants as specified in the study protocol. The nomenclature used in this context is that the trial is terminated for futility. Again, when there is compelling evidence that continuing to enroll participants into the trial does not have the possibility of providing useful information for the greater good, it is not ethically justifiable to expose additional participants to the small but nontrivial risks associated with any clinical trial.

A third reason for termination concerns the safety–risk dimension. If there is compelling evidence at the time of an interim analysis that the drug is unacceptably toxic, termination is appropriate. From the perspective of this book's discussions, the same logic would apply in cases where there was compelling evidence that the drug was acceptably safe, i.e., it is not associated with unacceptable cardiovascular risk.

6.4.2 Data Monitoring Committees

To facilitate interim analyses, a data monitoring process is necessary. This is typically performed by a data monitoring committee (DMC), sometimes called alternative names such as a data and safety monitoring board. Interim monitoring of accumulating data is an area of clinical trials that can be critical to the ethics, efficiency, integrity, and credibility of the trials and their conclusions, and increasingly such monitoring is conducted by formally established committees. The purpose of these committees is "to protect the safety of participants, the credibility of the study, and the validity of the results" (Ellenberg et al. 2003).

The composition of DMCs is typically multidisciplinary, and the participation of both clinicians and statisticians is critical. The DMC for a particular trial can be appointed by the trial sponsor or by a steering committee. Its duties can include reviewing the initial protocol, monitoring the conduct of the study by assessing accrual, eligibility, protocol compliance, losses to follow-up, and other issues concerned with safeguarding the participants and the integrity of the trial.

Before a trial starts, a charter needs to be written and agreed upon by the trial sponsor and the committee. This charter describes the structure and operation of the committee and specifies its activities and responsibilities. The DMC should have access to fully unblinded data, with actual treatments and not just codes available for its review. Except in certain limited circumstances, trial integrity is best protected when interim data comparing treatment groups are seen only by the DMC members and statisticians preparing the interim report (Ellenberg et al. 2003, see also O'Neill 2006).

6.4.3 Statistical Methodology for Interim Analysis

Statistical methods have been developed for interim analysis. Data-dependent stopping rules are established for each trial, stating under what circumstances the results of interim analyses will lead to the early termination of the trial. Data-dependent stopping is the process of evaluating accumulating data in a clinical trial and making a decision whether the trial should be continued or stopped because the available evidence is already convincing (Piantadosi 2005). These data-dependent stopping rules, along with the number and the timing of planned interim analyses, should be stated in the study protocol, just like any other aspect of the study design and methodology, and the statistical procedures to analyze the data at each time point should be specified in the associated statistical analysis plan. Each time an interim analysis is conducted, there will be more data available, since all data collected up to that time point are included in the analysis.

In the fixed sample clinical trial approach, one analysis is performed once all of the data have been collected. The chosen nominal significance level (the type I error rate), or α, will have been stated in the statistical analysis plan. This value is likely to be 0.05. In a group sequential clinical trial, the plan is to conduct at least one interim analysis and possibly several of them. This procedure will also be discussed in the trial's study protocol and/or the statistical analysis plan. For example, suppose the plan is to perform a maximum of five analyses (the fifth would have been the only analysis conducted had the trial adopted a fixed sample approach), and it is planned to enroll 1000 participants in the trial, of whom 500 will be randomized to the drug treatment group and 500 to the placebo group. The first interim analysis would be conducted after data had been collected for the first fifth of the total sample size, i.e., after 200 participants: this total of 200 participants would comprise 100 individuals from the drug treatment group and 100 individuals from the placebo group. If this analysis provided compelling evidence to terminate the trial, it would be terminated at that point. If compelling evidence to terminate the trial was not obtained, the trial would proceed to the point where two-fifths of the total sample size had been recruited, at which point the second interim analysis would be conducted. All of the accumulated data collected to this point, i.e., the data from all 400 participants (200 in the drug treatment group and 200 in the placebo group), would be used in this analysis.

Again, if this analysis provided compelling evidence to terminate the trial, it would be terminated at this point. If compelling evidence to terminate the trial was not obtained, the trial would proceed to the point where three-fifths of the total sample size had been recruited, at which point the third interim analysis would be conducted. If this analysis did not provide compelling evidence to terminate the trial, recruitment would continue to 800 participants, when the fourth interim analysis would take place. If this did not provide compelling evidence to terminate the trial, recruitment would continue to the full sample size of 1000 participants, when the fifth and final analysis would take place. Regardless of the outcome of this analysis, the trial would terminate at this point, since it was stated in the study protocol that 1000 participants were the maximum number that would be recruited.

By its nature, therefore, the group sequential design involves the possibility of multiple comparisons. In this example it is possible that five analyses could be conducted on data collected in this clinical trial. As was introduced in Sect. 4.4.1, there is an inherent problem with multiple testing. As more tests are performed, it becomes increasingly likely that a type I error will occur, i.e., that a result will erroneously be declared as statistically significant. As also noted in that chapter, fortunately the problem can be addressed completely satisfactorily by taking appropriate statistical care.

6.4.4 Subtle Difference in the Multiple Comparisons Approach in this Context

While similar in spirit to the approaches to the issue of multiplicity that were introduced in Chap. 4, the approach adopted in group sequential designs differs in its application. First, in the hypothetical examples presented previously, it was known before the clinical trials were conducted precisely how many multiple comparisons would be made: this number was equal to the number of pairwise comparisons of treatment groups that could be formed. That is, it is known in advance that for a trial involving three doses of a drug, three pairwise comparisons will be made and that for a trial involving five doses of a drug, ten pairwise comparisons will be made. In the example being used in this chapter, it is not known a priori how many pairwise analyses (interim analyses) will be done: the minimum number is one, and the maximum number (which is known a priori) is five.

Second, Tukey and Bonferroni multiple comparisons are done at the same point in time, i.e., immediately following a significant omnibus ANOVA result, and, more relevantly, are done with essentially the same amount of data in each case. The actual numbers of participants in each dose treatment group may be slightly different, but the amounts of data used in each comparison will be very comparable. In contrast, the number of data used in each interim analysis in our example increases linearly from the number used in the previous interim analysis. In our example, the number of data increases from 200 to 400, then to 600, then to 800, and finally to 1000 if the study is not terminated along the way.

Following the discussions of the technique of meta-methodology in the first part of this chapter, when it was noted that the availability of a larger data set enables more precise answers to be obtained than can be obtained by each of the smaller data sets contributing to the new data set created, you may intuitively feel that we would put more faith in the results of an analysis conducted on 1000 participants, somewhat less in the results of an analysis conducted on 800 participants, and decreasingly less faith in the results of the other three analyses, respectively. Therefore, there are two statistical considerations to be addressed in the case of interim analyses. First, the fact that more than one analysis may be done increases the probability of a type I error, and it is therefore appropriate to adjust the α-level in a more conservative direction. Second, it is usual to place more faith in an analysis conducted on a larger sample than on a smaller sample. Expressing this the other way around, which helps conceptualize the framework for the following discussions, it is usual to put less faith in an analysis conducted on a smaller sample than on a larger sample.

6.4.5 The O'Brien–Fleming Approach

While there are many statistical approaches to the issue of interim analysis, one notable strategy was suggested by O'Brien and Fleming (see Ellenberg et al. 2003). This approach modifies the α-level appropriate for each of the individual interim analyses in a trial by considering not only the total number of analyses that may be conducted but also the relative placement of each individual analysis in the string of possible analyses. The O'Brien–Fleming approach effectively makes it considerably harder for the result of the first interim analysis to attain statistical significance, as would a very conservative α-level, and relatively easier for the later ones to attain statistical significance, as would an α-level that approaches the one that would be chosen if there were only one analysis being performed, i.e., $\alpha = 0.05$. As Chow and Liu (2004) commented, this means that, when the early interim analyses are conducted on the relatively small amount of data that has been accumulated to date, the results must be extreme to justify recommending termination of the trial. In contrast, when later interim analyses are conducted using a sample size approaching the maximum planned sample size, the statistical criterion for deciding to terminate the study becomes progressively less stringent, approaching the one that would have been chosen for a fixed sample study employing the maximum number of possible participants.

6.4.6 Group Sequential Alpha Spending Functions

The original methodology for group sequential designs, and hence interim analyses, required that the number and timing of interim analyses be specified in advance. However, in cases where potentially unfavorable safety data may be emerging, a

more flexible implementation of the group sequential boundaries via an alpha spending function may be helpful. Waiting the planned length of time for the next look at safety data (perhaps 6–12 months) may not be a good idea if the previous interim analysis started to suggest unfavorable data.

An alpha spending function controls how much of the false-positive error, α, is used at each interim analysis such that no more than a predefined maximum total can be used by all the analyses taken altogether. When using an alpha spending function, the only thing that needs to be specified in the study protocol is the particular spending function that has been chosen. The precise number of interim analyses that may be conducted does not need to be specified in advance and neither does the exact timing of any given analysis. This means that a DMC can start out with a chosen alpha spending function and projected schedule for interim analyses but can then legitimately change the frequency and timing of the analysis as trends emerge as long as the predefined maximum α is not exceeded.

6.4.7 Ethical Considerations in Early Termination

We have noted previously that it is unethical to ask an individual to participate in a clinical trial whose design precludes any useful information being gained no matter how well the study is executed: this ethical issue has to be addressed before every trial commences. In the case of trials that may be terminated following interim analysis, ethical considerations need to be addressed for a second time when deciding whether or not to terminate a trial early. Deciding whether or not to terminate a trial is not as straightforward as might initially be hoped.

If compelling evidence of efficacy is found in an early interim analysis and the trial is therefore terminated, less safety data, particularly longer-term safety data, will be collected than would have been the case had the trial progressed to its completion. This occurrence is less problematic in cases where the drug is a treatment for a life-threatening disease or condition. Here, stopping the trial so that the participants in the control arm can also be administered the drug may be much more important than prolonging the trial and thus collecting more safety data in the trial itself. Safety data can be collected from the patients as therapy proceeds (the participants in the trial have now become patients under the care of a clinician since they are no longer experimental participants in a clinical trial).

In cases where it appears that the trial has little chance of demonstrating a drug's therapeutic benefit, and therefore the study team is considering terminating the trial for futility, several considerations are pertinent, including the following:

- Is it likely that this unfavorable trend might reverse itself? If the trial is stopped and the trend would have reversed itself, evidence of treatment benefit that would have been obtained will not be obtained and that treatment will not reach patients who might have benefited from it.

- While there is little likelihood of statistically demonstrating that the initially anticipated treatment effect will be seen, might it be the case that a smaller treatment effect will emerge that is still clinically significant?

In contrast, in cases where a drug is compellingly identified as unacceptably toxic, ethical considerations support termination in a clear manner.

6.5 Centralized Endpoint Adjudication

In the large cardiovascular safety outcome trials that are discussed in Chap. 13, it is of central importance to know how many cardiovascular adverse events occurred in each treatment group. However, the size and geographical distribution of these trials typically require the recruitment of participants at a large number of investigational sites located in many countries. Accordingly, there can be a considerable degree of variability in the "identification" of cardiovascular endpoints of interest since classification of events as "actual" study endpoints is a partially subjective process based on the application of a complex set of medical endpoint criteria to an often complex clinical event. Regulatory agencies therefore require the centralized adjudication of these events to control for the impact of this variability in "identification" and thereby to generate data for use in statistical analyses that are as standardized as possible.

A clinical endpoint committee is an essential component of this process. The dual purposes behind the implementation of centralized adjudication by these committees are to limit the number of individuals providing classifications of study endpoints to control for this variability and to employ experts to provide these classifications to achieve greater precision in the final classification of study endpoints. The committees are panels of independent experts charged with centrally reviewing and classifying suspected cardiovascular outcomes of interest in a blinded and unbiased manner, ascertaining whether they meet protocol definitions (endpoint criteria), and hence providing standardized endpoint outcomes for statistical analysis. Once a participant experiences one of these events, and the event is confirmed through centralized adjudication to meet protocol endpoint criteria, his or her endpoint data are included in analyses of the number of occurrences of the event for the respective treatment group. Committee members review overall participant data as well as endpoint-specific data, applying complex medical definitions to determine these adjudicated outcomes.

Committee-adjudicated outcomes typically either validate, negate, upgrade, or downgrade initial classifications of suspected endpoints. That is, the committee can agree with the event as reported by a site, disagree with it, or agree that an event happened but that it was more or less severe than judged by the site. Committee members can also identify new, previously unreported suspected endpoints for investigation and follow-up. Final committee-adjudicated outcomes are

not provided to investigators, since they have the potential to unduly bias investigator reporting of future suspected endpoints, and their intended use is for the purposes of performing uniform analysis of key clinical efficacy and safety variables. Final committee-adjudicated outcomes do not replace initial classifications, but they are the outcomes that are used to assess key variables in primary and secondary endpoint analyses. Differences between initial classifications by trial investigators and final committee-adjudicated outcomes should not be seen as a "failure" but rather a success: this is the expected result of any centralized adjudication process.

Independent, blinded, clinical endpoint committees are regularly commissioned to adjudicate potential cardiovascular endpoints in trials examining the efficacy of cardiovascular drugs as well as cardiovascular endpoints in cardiovascular safety outcome studies (see Seltzer et al. 2015).

6.6 Composite Endpoints

The occurrence of individual cardiovascular events of interest in cardiovascular safety outcome trials is often low. An extremely large number of participants are therefore needed to provide the statistical power necessary to identify a statistically significant difference between treatment groups in the rates of occurrence of a given event of interest. One way to increase the likelihood of finding a difference between the treatment groups if one truly exists is to use a composite endpoint. A commonly employed choice is the major adverse cardiovascular events (MACE) composite endpoint, comprising of nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death. An alternative is called MACE-plus. In this case, various other events such as unscheduled hospitalization for revascularization are included, each of which must also be specified in the study's statistical plan.

This approach reduces the number of study participants necessary to achieve the required statistical power in two ways. If the three individual components of the MACE composite endpoint (or the higher number of individual components in a MACE-plus composite endpoint) were compared separately between treatment groups, the numbers of events in each case would be lower than the total number of composite endpoint events. Moreover, a statistical correction would need to be made to address the issue of multiplicity: as more comparisons are made, the chances of "finding" a statistically significant difference that does not in fact exist, i.e., committing a type I error, increase (recall discussions in Chap. 4). To counter this possibility, the alpha level (typically 0.05 for a single comparison) used for each of the multiple comparisons must be lowered.

Using a composite endpoint, therefore, helps reduce the number of statistical comparisons of primary interest. If a trial's investigators are intent upon exploring a large range of endpoints, all of the other endpoints should be declared as secondary endpoints. It is common for statistical comparisons to be made for these secondary endpoints, but the degree of confidence that can be put in any individual "finding"

of a statistically significant difference between treatment groups is decreased. Such a "finding" should be thought of as an exploratory finding: it can then be legitimately investigated in a further trial(s) in which it becomes the primary endpoint.

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Part IV
Proarrhythmic Cardiac Safety

Chapter 7

The Proarrhythmic Cardiac Safety Regulatory Landscape Circa 2005–2015: Drug-Induced hERG Channel Block and the Thorough QT/QTc Study

One of the most feared complications in medicine is sudden death caused by drug-induced proarrhythmia. Accordingly, concerted efforts have been made to define a drug's proarrhythmic potential before regulatory approval (Link et al. 2010).

7.1 Introduction

The first step in the field of proarrhythmic cardiac safety is to determine to the greatest degree possible during nonclinical and preapproval clinical development whether a noncardiac drug has the propensity to lead to the polymorphic ventricular dysrhythmia *torsades* (Dessertenne 1966) in patients who may be prescribed the drug should it subsequently be approved for marketing. The second step is to remain alert to unexpected cardiac adverse drug reactions during its therapeutic use. This chapter's focus is the first step.

Drug-induced arrhythmogenesis can result in nonfatal dysrhythmias causing syncope, and on rare occasions it can prove fatal. Proarrhythmic cardiac safety concerns led to the marketing withdrawal of various drugs in the United Kingdom (UK) and the United States (USA) from the late 1980s to the early 2000s. These included terodiline (indicated for urinary incontinence, withdrawn from both markets in 1991), the antihistamine terfenadine (withdrawn from the US market in 1998), and levacetylmethadol (indicated for opiate addiction, withdrawn from the UK market in 2003) (Turner et al. 2013).

As first noted in Sect. 1.4.1, regulatory concern with these marketing withdrawals led to the release in 2005 of two ICH guidelines: ICH S7B, which focuses on nonclinical assessments of relevance to the proarrhythmic liability of noncardiac drugs (ICH 2005a), and ICH E14, which addresses preapproval clinical assessments and introduced the thorough QT/QTc (TQT) study that was discussed briefly in Sect. 5.5.1 when summarizing the relevant statistical considerations and techniques (ICH 2005b). ICH S7B is introduced in this chapter, and ICH E14 is discussed in greater detail.

J.R. Turner et al., *Cardiovascular Safety in Drug Development and Therapeutic Use*, DOI 10.1007/978-3-319-40347-2_7

The first part of this chapter's title, "The Proarrhythmic Cardiac Safety Regulatory Landscape circa 2005–2015," provides a clue that, as we write this chapter in January 2016, this landscape is in a state of transformation. As discussed in the following two chapters, initiatives are underway to modify both nonclinical and preapproval clinical assessments of a drug's proarrhythmic liability. Since an alternative approach in the preapproval clinical domain is closer to formal regulatory approval, this is discussed in Chap. 8: an alternative nonclinical approach is then discussed in Chap. 9. Nonetheless, the topic of this chapter, cardiac safety circa 2005–2015, remains of considerable importance. Events and regulatory science discussed herein address the origins of the formalized domain of proarrhythmic cardiac safety, a decade's work in this domain, and reasons why modifications to the ICH S7B and ICH E14 regulatory landscape have been deemed desirable.

7.2 A Brief History of Proarrhythmic Cardiac Safety

Table 7.1 presents a timeline of important events in the development of the current landscape, and, since methodologies and regulatory landscapes are evolving as we are writing this chapter, the potential future proarrhythmic cardiac safety regulatory landscape.

The development of the regulatory science employed in this field can be said to date back to the release in December 1997 of a "Points to Consider" document by the European Medicines Evaluation Agency (EMEA, now known as the EMA) which addressed the assessment of the potential for QT interval prolongation by noncardiovascular medicinal products (EMEA 1997). The field of proarrhythmic cardiac safety was formalized by regulatory agencies' adoption of ICH S7B and ICH E14. ICH E14 introduced the TQT study. A "Questions and Answers" document prepared by the ICH E14 Working Group containing questions and associated answers was released in June 2008, a revised version containing additional questions and associated answers was released in April 2012, and an additional revision released in March 2014. The third revision, referred to here as ICH E14 Q&A R3, was released in December 2015 (ICH E14 Q&A R3, 2015).

Across the last two decades or so, cardiac safety has been a major concern in the development, approval, and marketing of new drugs (Turner et al. 2013; Kothari et al. 2015), with a substantial number of drugs being restricted in their clinical application or withdrawn from the market due to adverse cardiovascular effects. There were 47 instances of postmarketing withdrawal of drugs between 1957 and 2007; 45 % of these were due to concerns regarding cardiovascular toxicity (Redfern et al. 2010). Similarly, 27 % of the potential new drug molecules that failed in nonclinical investigations in the last two decades did so because of cardiovascular toxicity (Turner et al. 2014). Consequently, significant attention has been focused on the prospective exclusion of unacceptable cardiovascular risk during drug development. The level of risk that is deemed acceptable differs based on the

Table 7.1 Timeline of important events in the evolution and employment of the thorough QT/QTc study as described in ICH Guideline E14

Date	Event
1997	The European Medicines Evaluation Agency's (EMEA's) Committee of Proprietary Medicinal Products released a "Points to Consider" document on the assessment of the potential for QT interval prolongation by noncardiovascular medicinal products (EMEA 1997)
1999	The FDA set up a working group and generated internal documents on QT assessment
2001	Health Canada submitted a concept paper to the FDA
2003	A joint Health Canada/FDA Concept Paper was circulated and the ICH process initiated
2005	ICH issued guidelines S7B and E14, which were adopted in Europe and the USA in 2005 and in Canada in 2006
2006	FDA established its QT interdisciplinary review team (IRT), which reviews protocols and study reports for thorough QT/QTc studies and advises review divisions accordingly
2006	Health Canada released regional guidance documents to support the interpretation and implementation of ICH E14
2008/2012/2014	The ICH E14 working group released a "questions and answers" document in 2008, which was expanded with additional questions and answers in a revised document issued in April 2012 and revised again in March 2014
2009/2010	The Japanese Pharmaceuticals and Medical Devices Agency (PMDA) adopted ICH E14 in 2009, allowing a year's "grace period" before its full implementation in November 2010
2015	The ICH E14 working group released the third revision of the "questions and answers" document associated with ICH Guideline E14 in December 2015 (ICH, 2015). This revision is triggering a major change in the cardiac safety regulatory landscape

disease for which a drug is being developed, the relative severity of the adverse cardiovascular effects, and the availability of safer therapeutically beneficial alternatives.

Among the possible cardiovascular risk liabilities, the risk of drug-induced *torsades* has been a major reason for the withdrawal of licensed drugs, accounting for around 26 % of drugs withdrawn from the market between 1990 and 2005 (Valentin 2010). This risk was not identified prospectively during the development of these drugs given the relative rarity of these events and the limited number of clinical trial participants studied in the preapproval period. However, a common thread which subsequently emerged in these cases was their association with prolongation of the QT interval component of the ECG. A stylized representation of the ECG, the QT interval, and QT interval prolongation was presented earlier as Fig. 3.2.

It was also apparent that these occurrences were concentration related and almost exclusively linked to delayed cardiac repolarization due to drug-induced inhibition of the rapid delayed-rectifier potassium current (I_{Kr}), the main repolarizing current

in ventricular cardiomyocytes (Hancox et al. 2008; Salvi et al. 2010). As discussed in Chap. 2, this current occurs due to an efflux of potassium ions through the I_{Kr} channel encoded by hERG, which is therefore also referred to as the hERG channel (Heijman et al. 2014). The idea therefore arose that the proarrhythmic liability of drugs could be prospectively investigated during drug development by using the degree (if any) of QT interval prolongation as a surrogate for their propensity to delay cardiac repolarization. Thus, the preapproval proarrhythmic cardiac safety testing paradigm described in this chapter came to be primarily based on the predictive link between drug-induced hERG channel blockade observed during in vitro nonclinical studies and QT interval prolongation in human participants in clinical trials.

7.3 Nonclinical Proarrhythmic Cardiac Safety Investigations: ICH S7B

The question of interest in this domain can be expressed as follows: can a nonclinical test, or more likely a battery of tests, correctly identify drugs that will, and will not, have a proarrhythmic liability in humans? Failing to identify a drug compound that is proarrhythmic in humans is far from desirable, but so is "identifying" a compound that would not have been proarrhythmic in humans, and thereby terminating a compound that potentially could have been an efficacious and acceptably safe drug. This point is discussed in more detail in due course.

Since its release in 2005, ICH S7B has governed the nonclinical proarrhythmic cardiac safety regulatory landscape. Two central components of this landscape are the in vitro hERG current assay and the in vivo QT prolongation assay. Although delay of repolarization can occur through modulation of several types of ion channels, inhibition of hERG current is the most common mechanism responsible for drug-induced QT interval prolongation and hence the focus of ICH S7B. The guidance listed the following objectives:

- Identify the potential of a drug molecule (and its metabolites) to delay ventricular repolarization.
- Relate the extent of the delayed repolarization to the concentration of the drug molecule and its metabolites.
- Elucidate the mechanism of action of the delayed repolarization.
- In conjunction with other relevant information, estimate the extent of delayed repolarization and QT prolongation in humans.

In vitro and in vivo methodologies can obtain information at several functional levels:

- Ionic currents measured in isolated animal or human cardiac myocytes (or cardiomyocytes), cultured cardiac cell lines, or heterologous expression systems for cloned human ion channels

- Action potential parameters in isolated cardiac preparations or specific electrophysiological parameters indicative of action potential duration in anesthetized animals
- Proarrhythmic effects measured in isolated cardiac preparations or animals
- ECG parameters measured in anesthetized or conscious animals

In vitro electrophysiology studies can provide information about the drug's effects on hERG current (and other cardiac ionic currents), thereby helping to identify cellular mechanisms of action affecting repolarization. Human cardiac ion channel proteins can be expressed in heterologous expression systems (noncardiac cells) to assess the drug's effect on specific individual ion channels in isolation from others (Leishman and Waldron 2006). hERG channels are typically heterologously expressed in Chinese hamster ovary (CHO) cells or human embryonic kidney cells. *Xenopus* oocytes have been used, notably as a demonstration of the hERG blocking action of terfenadine, but drug access may be limited in this assay, making mammalian cell lines and CHO cells preferable (Brown 2005).

An important concept in this context is the drug's half maximal inhibitory concentration (IC_{50}). The IC_{50} indicates how much of the drug is needed to inhibit specific biological activity in vitro by half. Considerable care must be taken in the assessment of IC_{50} since, in the determination of the safety margin, which puts hERG liability in context, it is divided by the effective therapeutic plasma concentration (ETPC) of the unbound drug. hERG IC_{50}/ETPC ratios greater than 50–100 are generally associated with drugs where the results from a TQT study are not of regulatory concern, and there is a lack of a QT liability during therapeutic use. While lower values of the ratio can be poorly predictive, the majority of drugs for which there are no reports of TdP in humans have ratios greater than 30 (Redfern et al. 2003).

7.3.1 An Example of a Battery of Nonclinical Tests

One example of a battery of nonclinical tests was proposed by Bass and colleagues in a 2008 publication discussing an initiative from the Health and Environmental Sciences Institute (HESI), a division of the International Life Sciences Institute (Bass et al. 2008). The authors noted that "the critical challenge in the pharmaceutical industry today is to identify experimental models, composite strategies, or biomarkers of cardiac risk that can distinguish a drug which prolongs cardiac ventricular polarization but is not proarrhythmic, from one that prolongs the QT interval and leads to TdP." They observed that a problematic feature of the biomarkers of proarrhythmic risk discussed in both ICH S7B and ICH E14 is their low specificity and hence "the potential for promising new test agents to generate false-positive results with a high frequency," an issue discussed in more detail in due course.

The paper by Bass and colleagues summarized the objectives of a workshop entitled "Moving towards better predictors of drug-induced Torsade de Pointes" that

brought together experts in the field to work collaboratively towards a better fundamental understanding of the emerging science, trends, and methodologies relating to the prediction of drug-induced TdP. These objectives included the following (Bass et al. 2008):

- Identify the mechanisms for drug-induced TdP to help develop better tools for identifying drugs carrying this liability.
- Evaluate emerging nonclinical methodologies for predicting drug-induced TdP.
- Identify biomarkers in nonclinical studies that may be applied to clinical testing for drug-induced arrhythmia.
- Identify critical aspects of nonclinical and clinical methods of evaluating the potential for drug-induced TdP in the context of public health decision-making.
- Identify short- and long-term priorities for developing better predictors of drug-induced TdP.

The authors concluded that there was a need for both in vitro and in vivo TdP proarrhythmia models to help increase knowledge of arrhythmogenic mechanisms and substantially improve the predictive value of a nonclinical battery of tests for the clinical proarrhythmic liability of new drugs. They proposed a multifaceted strategy employing test systems of increasing complexity (i.e., concurrently assessing several parameters at a time), including single cells, isolated cardiac tissue, isolated hearts, intact animals, and diseased animals.

7.4 Preapproval Clinical Investigations of Proarrhythmic Liability

Before discussing the TQT study in detail, it is appropriate to consider how ECGs are collected during the study and also how they are analyzed after the study has been completed. Both the acquisition of digital ECGs and their analysis require a combination of several logistical considerations, equipment-related procedures, and data management steps that the investigational site collecting the waveforms and the laboratory (lab) analyzing them must implement.

7.4.1 Collection of High-Fidelity Digital ECG Waveforms

Acquisition of high-fidelity digital ECGs is achieved in one of two ways: employment of a 12-lead resting ECG device that records 10-s strips of ECG signals or use of a 12-lead Holter device that records continuous ECG signals in ambulatory participants for 24 h or longer. At the time of drafting ICH E14, ambulatory ECG monitoring was not considered to be sufficiently well validated to be used as the primary methodology employed in the assessment of drug-induced effects on the QTc interval. Therefore, a significant number of early TQT studies used 12-lead resting ECG recordings. Given the advances in Holter ECG recording technology, it has been

demonstrated that Holter ECGs can be as accurate as 12-lead digital ECGs in the assessment of drug-induced changes in QT and RR intervals. Consequently, use of 12-lead Holter recorders in TQT studies steadily increased. TQT studies therefore now often employ Holter devices for collection of ECG waveforms, since this approach enables continuous digital waveforms to be recorded and short sections of 12-lead ECG strips to be extracted at prespecified study time points. This approach incorporates the advantage of selecting ECGs that are relatively free of artifacts and that are attained at a stable heart rate. Moreover, these 24-h recordings have a 50–100 times higher likelihood of detecting transient cardiac arrhythmias than conventional 10-s ECGs (Min et al. 2010).

The digital ECG waveform can be considered as a series of dots, with the precision of measurement afforded corresponding to the sampling frequency of the ECGs. Digital ECG recorders with a sampling frequency of 500 Hz (samples that are 2 msec apart) to 1000 Hz (samples are 1 msec apart) are optimal. In early TQT studies employing 12-lead Holter ECGs, the sampling rate employed was considerably lower, around 180 Hz, because of technological limitations at that time. However, Holter recorders used more recently have sampling rates of 500 Hz and 1000 Hz, equal to those of 12-lead resting ECG devices (Panicker et al. 2010).

Consistency in operator techniques relating to skin preparation, ECG lead placement, and the study participants' position are important components of the collection of good-quality ECGs, since inconsistencies in recording methodology add to variability in ECG parameter values. Site training to provide clear instructions that ensure participants rest in a supine position for several minutes prior to the ECG acquisition time points to ensure a stable resting heart rate is essential: otherwise, activity-related heart rate changes could be falsely attributed to the study drug. Additionally, ECG recording must precede the drawing of blood for pharmacokinetic (PK) samples for exposure–response analysis, a topic discussed in the following chapter.

In studies using 12-lead resting ECG devices, the digital ECG files recorded at the site are transmitted via an in-built modem to the ECG receiving system on the server of the lab where they will be analyzed. After the confirmation of demographics, ECG files are converted into FDA-compliant Extensible Markup Language (XML) files that are conveyed to the ECG analysis software at the lab. When employing 12-lead Holter devices, the digital ECG data are recorded on a removable memory card that may be sent via a courier to the lab. The digital Holter file is downloaded and used for the extraction of discrete 10-s ECG files that are analyzed by a process similar to that used for 12-lead resting ECG. Alternatively, the digital Holter recording from the removable memory card may be transferred to the investigational site computer and transmitted to the lab's server via a secure web upload.

7.4.2 The Core ECG Lab

The labs that analyze ECGs collected during a TQT study are highly specialized for this purpose and are referred to as core ECG labs. This nomenclature is similar in intent to the term central lab: central labs are used to analyze different types of

biological samples (e.g., blood and urine) taken during many large clinical trials. The name central lab refers to testing labs to which samples from all of the investigational sites in a clinical trial are shipped. This strategy has two important advantages compared with using a large collection of local labs, i.e., laboratories close to each investigational site:

- Assurance that the lab conducting the analyses of the samples is compliant with current good clinical practice (cGCP) is much easier.
- Statistical difficulties associated with analyzing pooled lab data are avoided.

cGCP guidances require that all labs have data-audit trails, standard procedures, trained staff, archives of samples and data, and routine quality assurance inspections (Prokscha 2007). If multiple labs were used, assurance would be required that cGCP requirements were met at every one. Use of a single central lab makes assurance of cGCP much simpler.

Analysis of data that have been collected from many sources and then pooled into one data set can lead to considerable statistical problems. Since the majority of lab measurements are surrogates and reference ranges can vary from analytical method to method, many different types of errors can occur during lab testing. These can be due to variation in many aspects of data collection, including the technician, an instrument, the environment, and the reagents used. While statistical approaches to standardize values from several local laboratories, each with their own reference ranges, have been described (Chuang-Stein 1992), central labs provide a real statistical advantage: all samples are analyzed in the same manner in the same laboratory, thereby providing a much greater degree of fidelity. Thus, the role of the ECG core lab is not restricted just to ECG analysis as discussed in the next section but also encompasses aspects of ECG acquisition and processing as well as submission of the annotated digital ECG data to regulatory agencies.

7.4.3 Analyzing ECG Waveforms in a Core ECG Lab

ICH E14 recognizes that the threshold of regulatory concern in a TQT study is small, i.e., a mean QT prolongation of about 5 msec. Given that the length of a "typical" QT interval is in the order of 400 msec, the increase of interest is in the order of 1 %. Detecting such a small change requires a high degree of accuracy and precision in ECG measurement. ICH E14 recommends skilled readers without specifying the specific training needed. A technician performing the initial read followed by a cardiologist overread is considered adequate. It is the responsibility of the core lab to have appropriate criteria for reader selection and training and benchmarking their competence (Panicker et al. 2009). ICH E14 further states that the ECGs must be analyzed by a small number of readers and that all ECGs from the same participant be read by the same reader (blinded to treatment arm) to maintain consistency in QT measurement. A specific assessment of reader variability is also required, with a subset of the ECGs being reread to quantify inter- and intra-reader variability. Each core lab should have a well-defined approach to quantifying reader

variability (Salvi et al. 2014). Without appropriate care, a QT interval measured in the same ECG by the same reader blinded to his or her previous measurement may vary up to 25 msec (Malik and Camm 2001).

The method of QT interval measurement is also of great importance (Salvi et al. 2010). ICH E14 recognizes that there are several different methodologies for the measurement of ECG intervals which differ in "what to measure" in terms of items and characteristics including conventions for lead selection, waveform presentations, definition of T-wave offset, and handling of U-waves. It is not prescriptive about the method chosen but emphasizes the need to use a consistent approach. In this context, the use of a positive control such as moxifloxacin, a drug whose effects on ECG waveforms are very well known, is an internal validation of the QT interval measurement methodology and the accuracy of the ECG readers.

A core lab's ECG analysis system also enables various techniques of measurement. ICH E14 recommends one of the following approaches for TQT studies:

- Fully manual method. Identification of waveforms and placement of fiducials (the onset of the QRS complex and the offset of the T wave) are performed entirely by the human reader without any assistance from a computer.
- Manual adjudication (semiautomated/computer assisted). Initial identification of waveforms and placement of fiducials are performed by a computer algorithm. This is followed by a 100 % overread by humans who can either accept or alter the placement of fiducials as deemed appropriate. This approach is most commonly used.

Regardless of which technique is used, readers should be trained in, and follow, standard operating procedures with prospectively defined criteria on how to place or correct fiducials for interval measurement. Although fully automated methods are available and offer the advantage of being consistent and reproducible, they have not yet been sufficiently validated and can yield misleading results, especially for less-than-good-quality ECGs and in the presence of morphologic or rhythm abnormalities. However, with improvements in computer algorithms, there are now validated computer-assisted techniques, often described as highly automated reading, wherein intervals are measured by a computer algorithm that also provides confidence scores based on the quality, morphology, and measured values. Only select ECGs exceeding prespecified quality cutoffs then undergo human overread. The ECG readers also manually assess the shape of the T wave for any drug-induced changes and for the presence of other diagnostic features such as cardiac arrhythmias and conduction abnormalities. A combination of validated technology solutions, trained readers, and scientifically rigorous methods is therefore essential to ensure high-quality ECG data.

7.4.4 Adjusting QT Measurements for Heart Rate

QTc values are used in analysis of potential drug-induced QT interval prolongation, where the "c" stands for corrected for heart rate. Many correction factors have been developed to address this issue (see Camm et al. 2004). The more commonly used correction factors, QTcB (Bazett's correction) and QTcF (Fridericia's correction)

employed in this manner date back almost 100 years in the context of clinical practice.

When discussing the history of the reasons behind the choice of the preferred formula for adjusting QT interval values, Camm and colleagues commented as follows (Camm et al. 2004, p 44):

> Of all the formulas used in the past, the most commonly used are Bazett's square-root formula ($QTc = QT/RR^{1/2}$) and Fridericia's cube-root formula ($QTc = QT/RR^{1/3}$). Between the two, Bazett's formula is more commonly used [in clinical practice] and most reported values are given using Bazett's formula because of its simplicity (most simple calculators have a function for a square root but not for a cube-root computation, which gives a practical advantage to Bazett's over Fridericia's correction).

Bazett's correction is still the most commonly used correction factor in clinical practice: most ECG machines used in clinical practice settings automatically provide this correction.

Bazett's and Fridericia's corrections essentially aim to normalize the QT interval to a heart rate of 60 bpm. The nomenclature (and notation) used for these two corrections is as follows, where RR is the interval between the R wave of one ECG and the R wave of the subsequent ECG:

$$QTcB = \frac{QT}{RR^{1/2}} = \frac{QT}{\sqrt{RR}}$$

and

$$QTcF = \frac{QT}{RR^{1/3}} = \frac{QT}{\sqrt[3]{RR}}$$

ICH E14 proposed that several values should be reported when presenting the results from a TQT study. These include the following:

- The actual (uncorrected) QT interval
- Heart rate
- QTcB
- QTcF
- QT corrections of any other type should the researchers wish to employ additional correction factors

However, QTcB is now widely accepted to be an inferior method of correcting for heart rate, and using QTcF is considered appropriate in most situations.

An alternative correction employs linear regression techniques to normalize the QT interval to a heart rate of 60 bpm. ICH E14 discusses a correction calculated in this manner in the Framingham study (see Kannel and Sorlie 1975; Tisdale, et al. 2007). Regression approaches can also be used from other large databases in a similar manner: employing pretreatment data from a study, QT interval measurements

are regressed on (1-RR) to obtain estimates of the slope for the following equation:

$$QTc = QT + b(1 - RR)$$

Another correction methodology employs linear regressions that are calculated for each individual participant in a TQT study: this methodology yields the individual corrected QT or QTcI. Pretreatment QT and heart rate data are used to fit a separate regression for each participant. This means that a slope coefficient is applied to each participant on an individual basis, rather than using the same coefficient in a population-level regression approach. The employment of QTcI has been advocated as the primary endpoint in TQT studies where the drug being tested is known to exert notable influence on heart rate. However, when QTcI is employed as the primary endpoint, it is good practice to report QTcB (for historical reasons) and QTcF as well (Litwin et al. 2008).

7.5 Further Discussion of ICH E14 and the TQT Study

The TQT study was discussed to a certain degree in Chap. 5 so that the related hypothesis-testing statistical methodologies, the union–intersection test and the intersection–union test, could be placed in this context. The explicit objective of the TQT study is to provide an accurate and precise estimate of a drug's effect on the QTc and, based on this assessment, to guide the extent of ECG monitoring that will be needed in Phase III (Bloomfield 2015). At this point it is appropriate to recap the key points of the TQT study's traditional design before presenting new material discussing the TQT study in more detail.

As noted at the beginning of this chapter, the first goal of the field of proarrhythmic cardiac safety is to determine to the greatest degree possible during preapproval research whether a noncardiac drug has the propensity to lead to torsades in patients who may be prescribed the drug should it subsequently be approved for marketing. As represented in TQT studies, which are typically conducted in clinical pharmacology units within residential or inpatient medical centers to facilitate 24-h supervision and extensive monitoring of participants' health status in addition to the collection of the necessary ECG waveforms, QTc prolongation is considered as a biomarker for torsades. Therefore, the purpose of the TQT study is to prospectively exclude an unacceptable degree of drug-induced QTc interval prolongation.

The TQT study is a randomized, placebo- and positive-controlled clinical trial that can adopt a crossover design or a parallel-group design. The traditional four treatment arms are as follows:

- A positive control arm, comprising of a drug that is known to increase the QT interval by around 5 msec. This is employed to establish assay sensitivity, i.e., to

demonstrate that the methodology employed is able to detect a prolongation of the QTc interval when it is indeed present.
- A placebo arm, against which the drug is compared.
- The proposed therapeutic dose of the drug.
- A supratherapeutic dose of the drug: unless the proposed dose is close to the maximum tolerated dose, the supratherapeutic dose is likely to be several multiples of the proposed dose.

The choice of a crossover design (in which each participant receives all four treatments in a specified sequential order) or a parallel-group design (in which each participant receives only one treatment and which therefore necessitates four times as many participants) should be considered carefully. The primary advantage of the crossover design, which is chosen more often than the parallel design, is that each participant serves as his or her own control, thereby reducing the inter-participant variability for estimates of the drug's effects on the QTc interval. A direct corollary of this reduction in variability is that a smaller sample size is required for an appropriately statistically powered study. It is advisable to use balanced crossover designs, in which each treatment is administered to some participants prior to every other treatment, to ensure that any crossover effect is balanced. However, crossover trials are typically not recommended when the test drug has a long half-life (and hence requires long washout periods) or when multiple doses are being evaluated: in these instances a parallel-group design may be considered advantageous (Turner and Durham 2009).

TQT studies are typically conducted at some point following completion of single- and multiple-ascending dose (SAD and MAD) studies and others such as renal impairment, hepatic impairment, and drug–drug interaction studies, which help determine the supratherapeutic dose, frequently the most difficult choice in TQT study design (Turner et al. 2015). Optimal TQT study design requires fundamental knowledge of the drug's clinical pharmacokinetic profile, including estimates of C_{max} and T_{max}, since QTc prolongation must be assessed shortly before, at, and shortly after T_{max} in addition to some later time points: these typically include 24 h after drug administration and additional later time points should the drug have late-appearing metabolites that may themselves have a proarrhythmic influence.

7.5.1 Statistical Analyses Discussed in ICH E14

The statistical details of the intersection–union and union–intersection tests used in the analysis of QTc data following the completion of a TQT study were provided in Chap. 5 since we believe that readers interested in that level of detail should have access to it within this book. That said, our discussions in this chapter are couched in more simple nomenclature.

ICH E14 noted that "The QT/QTc interval data should be presented both as analyses of central tendency (e.g., means, medians) and categorical analyses. Both can provide relevant information on clinical risk assessment" (ICH 2005b).

Categorical analyses, which are descriptive in nature and the simpler of the two sets of analyses, are discussed first.

Categorical analyses are based on the number and percentage of participants that meet or exceed a predefined upper limit. Such limits can be stated in the study protocol or the associated statistical analysis plan in terms of absolute QTc interval prolongation values or change from baseline. At the time of the guidance's release, there was no consensus concerning the best choice of these limits. The guidance therefore suggested that multiple analyses using several predefined limits were a reasonable approach in light of this lack of consensus. For absolute QTc interval data, the guidance suggested providing absolute numbers and percentages of subjects whose QTc intervals exceed 450, 480, and 500 msec. For change-from-baseline QTc interval data, the same information might be provided for increases exceeding 30 msec and those exceeding 60 msec.

Now, consider the second part of the overall analytical strategy, which ultimately focuses upon the mean QTc prolongation induced by a test drug. The first aspect of this part is the demonstration of assay sensitivity. Moxifloxacin, given as a single oral dose of 400 mg, is the typical choice of positive control (other possibilities have been discussed in the literature, e.g., see Taubel et al. 2010). Moxifloxacin is an 8-methoxyquinoline antibacterial with enhanced potency against important gram-positive pathogens, notably *Streptococcus pneumoniae* (see Burkhardt and Welte 2009; Albertson et al. 2010; Tulkens et al. 2012; Chuchalin et al. 2013; Kuzman et al. 2014). Moxifloxacin-induced QTc effects have been reported in the literature (e.g., see Yan et al. 2010). The pharmacokinetic properties and QTc time-course profile of moxifloxacin are well characterized: the profile includes a rising phase, a peak around 2–4 h postdose, and a tapering phase. Litwin and colleagues (Litwin et al. 2008) cited an average moxifloxacin-induced increase in the QT interval of 5–8 msec: other authors have suggested slightly higher values.

To investigate assay sensitivity, the change from baseline QTc after administration of the positive control and the change from baseline following placebo are obtained. Assay sensitivity is tested by placing the lower bound of a one-sided 95 % CI on the mean difference point estimate (moxifloxacin minus placebo) for each time point. Assay sensitivity is demonstrated if the lower bound for any of the time points is greater than 5 msec. Such an occurrence provides compelling statistical evidence that the study design and methodology are sensitive enough to detect QTc prolongation induced by the investigational drug if it truly exists.

If assay sensitivity is demonstrated, the second aspect is to determine if the regulatory "threshold of concern" for drug-induced QT interval prolongation as described in ICH E14, which is "around" 5 msec, has been breached or not. This aspect is statistically operationalized by placing the upper bound of a one-sided 95 % CI on the mean difference point estimate (test drug minus placebo) for each time point for both the therapeutic and supratherapeutic doses. If no upper bound exceeds 10 msec, the study is termed "negative," and no additional regulatory scrutiny falls on the drug: ECG assessments in subsequent Phase III trials will be typical for any drug in its class. If any upper bound breaches 10 msec, the study is termed "positive." In this case, more extensive and intensive ECG/QT evaluations will typically occur during the rest of the drug's development than would usually occur for a drug in its class.

7.5.2 Nomenclature Considerations

The nomenclature "negative" and "positive" deserves further comment. As Satin and colleagues (2011) observed, "Interpretation of the results of a TQT study is more subtle than the dichotomous terms *negative* and *positive* suggest." The greater the overall degree of QTc prolongation, the greater the regulatory concern, and, as just noted, a positive study will likely mean that the drug's sponsor will be expected to conduct more extensive cardiac monitoring in later clinical trials. However, since a drug-induced increase of 10 msec or more does not precisely equate to the drug being proarrhythmic, it does not necessarily equate to the drug failing to receive marketing approval. Regulatory agencies employ benefit–risk analysis in their marketing approval decisions, analysis that can also factor in information about the severity of the indication and the current availability or not of other drugs for the same indication as well as information specific to the drug under consideration: the greater the severity of the drug's indication and the fewer currently available treatments there are for it, the more likely a drug is to be approved for a given degree of QTc prolongation over and above the 10-msec threshold. By the time they make such decisions, regulatory agencies have an enormous amount of data to inform each decision, i.e., data on the specific drug and data on any other drugs already approved for the indication. In this context, QTc prolongation would be one of potentially several risks against which a new drug's benefits are weighed. If approved, the drug's labeling will carry information for physicians and patients concerning its degree of QTc prolongation.

7.6 Additional Considerations Pertaining to TQT Studies

The descriptions in the preceding section apply to the "traditional TQT study." Other considerations, however, are also pertinent, particularly as they tie into later discussions in Chap. 10 concerning the cardiotoxicity of many oncologic agents.

7.6.1 Being "as Thorough as Possible" When a Formal TQT Study Is Infeasible

As we have seen, the traditional TQT study contains a placebo arm. In cases where the study is conducted using healthy participants, there is no ethical concern: by definition, these individuals do not have a disease requiring treatment. However, placebo treatment (alone) is not an ethical option in certain circumstances. Rock et al. (2009) therefore discussed alternate approaches when optimum ones are infeasible. Consider the case of developing oncologic drugs. It is well known that many of these drugs are toxic and that cardiotoxicity is relatively common. Therefore,

they cannot ethically be given to healthy individuals: since such individuals cannot gain any benefit from them, the benefit–risk balance of administering such a drug to them is immediately unfavorable, no matter how small the risk of toxicity (see Lee and Turner 2016, for additional discussions). However, this does not immediately exempt such drugs from some form of evaluation for QTc prolongation liability: when a TQT study cannot be performed, another form of evaluation that is as thorough as possible must be employed. An alternate approach is therefore to conduct a modified form of the TQT study in which individuals with cancer are the study participants. They will already be treated for their disease, likely with the best available therapies, regimens called standard of care. Therefore, the various treatments that are administered in the evaluation of the test drug's QTc prolongation liability will be added on to the medications the participants are already taking.

Similarly, a traditional approach may not be optimal for macromolecules such as therapeutic proteins since ICH E14 focused on proarrhythmic liability assessment for small-molecule drugs: accordingly, Rodriguez and colleagues (2010) provided discussions of potential approaches in development programs of therapeutic proteins.

7.6.2 Correcting for Heart Rate Is Not as Simple as It May Initially Appear

In addition to the issue of determining which correction formula is most appropriate in any given circumstance (i.e., which one should be declared a priori in a study's statistical analysis plan as the primary correction methodology to be employed), the phenomenon of hysteresis is also problematic. It has already been noted that QT is related to heart rate in an imperfect nonlinear manner. A further complication is that the change in QT lags behind the change in heart rate that leads to it, and this delay can approach several minutes. This delay in the accompanying QT change has the consequence that the same QT change is not always associated with the same heart rate, and hence using the same heart rate to correct different QT values leads to more than one associated QTc value.

Consider the example of heart rate increasing from 60 to 80 bpm over a period of time. At the point when heart rate is 70 bpm, the QT interval will not have adapted (in this scenario the adaptation is a shortening of the QT interval) as much as it would if the heart rate had been at a steady rate of 70 bpm for some time. Now consider the example where heart rate decreases from 80 to 60 bpm over a period of time. At the point when heart rate is 70 bpm, the QT interval will not have adapted (in this scenario the adaptation is a lengthening of the QT interval) as much as it would if the heart rate had been at a steady rate of 70 bpm for some time. Correcting the two QT values measured at a heart rate of 70 bpm in these two cases, i.e., two different QT values, will therefore result in two different QTc values for the same heart rate, something that defeats the point of correcting for heart rate in the first place.

Another fundamental problem with QTc measurements is that there is a lot of variation, i.e., considerable differences of values within a given data set. As Mason (2008) noted in this context, variance makes it more difficult to determine if an observed change in QTc is actually due to a drug effect. Biological sources of variance in QTc include autonomic influences, circadian influences, disease states, food, environmental influences, and gene variants. The correction procedure itself can also lead to variance due to inadequate correction formulae and hysteresis and also due to measurement-induced variance by both the methodology employed and the readers determining QT values from the recorded ECGs (Mason 2008). Anything that can be done to reduce variance leads to improved statistical power, which in turn means that less participants in the TQT study are needed (if the same number of ECGs is obtained per participant) or less ECGs per participant need be recorded.

One ideal scenario is one in which heart rate does not change: in this case no correction for heart rate is required. However, this is not always possible or practical: some drugs may have a sizeable effect on heart rate, and maintaining a precisely level heart rate in humans is difficult (although heart rate pacing may be possible in some animal models). Because of these difficulties, it may be helpful to find an index of torsadogenic liability that is independent of heart rate, i.e., one where the heart rate at the time of the index's measurement does not need to be known.

Garnett and colleagues (Garnett et al. 2012) discussed the issue of QT interval measurement correction for drugs that have a substantial direct or indirect effect on heart rate. Descriptions and applications were provided for individualized QT–RR corrections, Holter bin and dynamic QT beat-to-beat methodologies, pharmacokinetic–pharmacodynamic modeling, and QT assessment at constant heart rate. As the authors noted, an important study design element in such investigations is the collection of drug-free data over the range of heart rates that are expected to be seen on treatment.

7.6.3 Potential Replacements for the Active Pharmacological Control Treatment Arm

Several potential replacements of the active pharmacological control treatment arm in a TQT study with another means of establishing assay sensitivity have been discussed in the literature. One example is the detection of food-induced QTc shortening (Taubel et al. 2012; Hnatkova et al. 2014).

7.6.4 Study Design Considerations: Optimizing Statistical Power

We noted previously that both crossover and parallel-group designs can be employed in TQT studies. As in any other clinical trial, the issue of statistical power is of interest. When commenting on the topic, Mayo (2009) observed as follows: "The

greatest limitation on the design of [randomized clinical trials] is usually not money, investigators, or facilities, but number of subjects. If too few subjects are recruited into the trial, other design features cannot compensate, and the trial will fail." While the comments were made in the context of trials designed to investigate a test drug's efficacy, which typically employ many more participants that TQT studies, the fundamental question holds true in this context too: when conducting a TQT study, a sufficient number of participants are necessary to provide the necessary statistical power to exclude a 10-msec QTc prolongation if the drug truly does not carry a QTc liability.

The topics of statistical power and sample size estimation are intimately related. A critical part of study design is deciding upon the number of participants that will be employed in the trial. Readers are referred to other sources for detailed discussion of these topics (e.g., Turner 2010; Teare et al. 2014; Greene 2015; Jia and Lynn 2015): at this time, pragmatic descriptions are sufficient.

Several statements can be made regarding statistical power:

- The greater the number of participants, the greater the power.
- The greater the number of readings taken per participant, the greater the power.
- The greater the degree of precision in the measurements taken, the greater the power.

Given the first two statements, a perfectly reasonable initial extrapolation is to consider recruiting a very large number of participants and taking many readings per participant. In the real world, however, such a strategy is limited by resources, since the more individuals that are recruited into the trial, the longer the trial may take to complete and the greater the cost will be. Therefore, the statisticians conducting the sample size estimations carefully balance multiple considerations to come up with a number of participants, and a number of readings per participant, that they believe will provide an acceptably high power to exonerate the drug from an unacceptable QTc liability if such a liability is truly absent while at the same time not devoting inordinately more resources to the study than are needed.

The third statement addresses precision of measurement: the more precise the measurements, the lower the inter-participant variability will be, and the lower the number of participants that is needed to achieve a desired statistical power. Precision of measurement is therefore of great interest.

With regard to the study design and statistical issues summarized here, the following authors have offered a representative overview of work in this area: (Malik et al. 2004, 2008, Hnatkova et al. 2006, Zhang and Machado 2008, Zhang 2011, and Zhang and Stockbridge 2011). A related topic is exploration of highly automated reading systems. These systems conduct the necessary analyses much more quickly (itself a considerable advantage) and putatively involve less variation in reading, which translates to greater statistical power. The following authors have addressed this topic: (Fosser et al. 2009, Couderc et al. 2011, Sano et al. 2014, and Mason and Moon 2015).

7.7 Limitations of this Paradigm

Even given all of these considerations, we are nonetheless left with the fundamental tenet that the TQT study employs QTc prolongation as the biomarker of proarrhythmic risk. There is widespread acknowledgement that QT interval prolongation is not the most accurate predictor of such risk. Indeed, some researchers have commented that if it were not relatively easy to measure (at least theoretically, precise identification of the offset of the T wave can be very difficult for some waveforms), it may have been discarded all together some time ago.

The title of this chapter, "The Proarrhythmic Cardiac Safety Regulatory Landscape circa 2005–2015: Drug-induced hERG Current Block and the Thorough QT/QTc Study," provides a clue that, as we write this chapter in December 2015, this regulatory landscape is in a state of flux. The proarrhythmic cardiac safety paradigm discussed in this chapter has undoubtedly been successful in one important sense of the word. Before the adoption of the paradigm, 14 drugs were removed from the market worldwide (Johannesen et al. 2014). In contrast, since the paradigm's implementation in 2005, no drug with unanticipated potential for torsades has entered the market. However, overemphasis of the surrogate markers in this paradigm has had important limitations and is believed to have adversely impacted the development of potentially valuable therapeutics and also increased the cost of developing safe drugs considerably (Bouvy et al. 2012). While protection of public health by preventing drugs with unfavorable benefit–risk balances getting to market is of clear importance, so is promotion of public health by enabling drugs with favorable benefit–risk balances to reach market approval.

Increases in QTc are highly sensitive but not very specific for predicting ventricular proarrhythmia risk. In the statistical realm, sensitivity measures the proportion of true positives that are correctly identified as such. In this context, it refers to the ability of the paradigm to identify correctly drugs that have a true QTc prolonging liability. As noted earlier, the paradigm does very well in this regard. Another term, specificity, refers to the ability of the paradigm to identify correctly drugs that do not have a true QT prolonging liability. Unfortunately, the paradigm does not do well in this regard: its low specificity means that there is the potential to frequently "identify" a drug that does not have a true proarrhythmic risk as having this risk. This occurrence is known as a false positive. This paradigm may therefore be inappropriately assigning torsadogenic liability to many drugs: de Ponti estimated that "as many as 60% of new molecular entities developed as potential therapeutic agents, when assayed for IKr blocking liability, test positive and are thus abandoned early in development" (de Ponti 2008).

The degree of QTc prolongation, with the exception of pure I_{Kr} blockers, is largely drug specific, and QTc can be prolonged by many factors not associated with proarrhythmia (e.g., other drugs, autonomic perturbations, glucose/insulin levels, circadian rhythms). The paradigm described in this chapter may therefore have had the unintended consequences of propagating an inaccurate understanding of the

safety risk associated with hERG channel and/or QTc signals. The perception that detection of even a small effect on I_{Kr} or mild QTc prolongation will result in adverse regulatory and commercial implications during drug development has significantly impacted the pharmaceutical discovery pipeline. Such findings may have resulted in the de-emphasis of early drug candidates, redesign of chemical structures to address perceived safety concerns (possibly resulting in reduced efficacy or poorer pharmacokinetic profiles of subsequent drug candidates), inability of smaller companies to out-license or get funding for drugs that would have an overall positive benefit–risk profile despite having an identified QTc liability, and, ultimately, inappropriate discontinuation of entire development programs with potentially significant public health benefits.

7.7.1 Thoughts from FDA Regulators

Zhang and colleagues from the FDA published a paper in May 2015 entitled "Lessons Learned from Hundreds of Thorough QT Studies" (Zhang et al. 2015). They shared their thinking on how sponsors might have (mis)interpreted the intentions of the regulatory landscape described in this chapter. As noted in Sect. 7.6, unless the proposed dose of the test drug is close to the maximum tolerated dose, the supratherapeutic dose chosen in a TQT study is likely to be several multiples of the proposed dose. As Morganroth (Morganroth 2005, p. 209) noted, the supratherapeutic dose "should be modeled based on the known pharmacologic properties of the drug and how the extent of exposure will change when it is taken by a patient who has effect modifiers." As a guideline, Morganroth also suggested that it should be at least 3–5 greater than the size of the proposed clinical dose and that for some agents, such as antihistamines and antibiotics, it should be over ten times greater. A similar order of magnitude of 3–10 times the proposed clinical dose was cited by Zhang and colleagues (Zhang et al. 2015).

However, Zhang and colleagues noted that, in real life, sponsors are "reluctant to choose the highest tolerated dose for their TQT studies." This reluctance has stemmed from sponsors' intimidation by the 10 msec threshold of regulatory concern, even though, from the FDA's perspective, "10 ms is not a magic number." The authors continued as follows: "For instance, if the largest upper bound at the maximum tolerated dose is 11 ms, even though we cannot conclude that the study is negative, we do not claim that the study drug is proarrhythmic automatically without further investigation." Indeed, sponsors were encouraged to submit "positive" TQT studies for further evaluation since "a good compound should not be terminated based only on the outcome of a TQT study" (Zhang et al. 2015). The authors noted, however, that they suspected "sponsors discontinue further drug development of some promising compounds even before submission to the agency due to concerns over QT signals."

7.8 QTc–Concentration Relationship Analysis as an Adjunct to the TQT Study

As Garnett and colleagues observed, the ICH E14 criterion for assessing drug-induced QT prolongation "does not explicitly account for individual drug concentrations" (Garnett et al. 2008). However, the authors also noted that experience with reviewing QT studies "indicates that understanding the relationship, if any, between individual drug concentration and QT change provides important additional information to support regulatory decision making. Therefore, regulatory reviews of 'thorough QT' studies routinely include a characterization of the concentration-QT relationship." The authors provided examples to illustrate how the QTc–concentration relationship has been used to plan and interpret TQT studies, to evaluate QT risk for drugs for which TQT studies have not been conducted, to assess QT risk in subpopulations, to make dose adjustments, and to write informative drug labels. Recent developments in this domain are discussed in the following Chap. 8.

7.9 Other Potential Indices of Proarrhythmic Liability

Drug-induced prolongation of the cardiac action potential does not occur uniformly throughout the heart. Shah (2005) noted that it is likely that differential effects of a drug on different tissue types within the ventricles play an essential role in the generation of *torsades*: drugs that have differential effects on epicardial, mid-myocardial, and endocardial myocytes are particularly prone to inducing *torsades* since regional differences can lead to arrhythmogenic spatial dispersion of repolarization (Shah 2005, p. 275). This transmural dispersion of repolarization (TDR) is difficult to quantify in the conventional ECG, and one possible indicator is the interval between the peak and the end of the T wave: it can be notated in various ways, including Tpeak–Tend, TpTe, and the Tpe interval (Gellert et al. 2014; Maury et al. 2015): this indicator "has excellent repeatability supporting its use as a supplement to QT in observational and clinical studies" (Gellert et al. 2014). Presence of a notched or biphasic T wave could be another indicator, with the first part of the T wave representing repolarization of one population of cardiac cells and the second part representing repolarization of cardiac cells with a prolonged action potential.

Increased TDR is "an abnormal increase in the differences in action potential duration across the ventricular wall, between the left and right ventricles, or between the base and apex of the heart" (Lagrutta and Salata 2006, p. 458). These authors further hypothesized that an increase in TDR in the ventricle is the substrate of *torsades*.

Assessment of T-wave morphology may also provide relevant information. Vincente and colleagues (Vicente et al. 2015) noted that patients with LQT2 can develop flat, asymmetric, and notched T waves while also noting that we do not know how additional block of calcium or late sodium channels, which decrease

proarrhythmic risk, affect T-wave morphology. These authors compared the effects of dofetilide, a pure hERG channel blocker, with those of quinidine, ranolazine, and verapamil, drugs that also block calcium or sodium channels. Dofetilide and quinidine, which leads to strong hERG block in conjunction with lesser calcium and late sodium block, led to substantial changes in T-wave morphology. Ranolazine, which leads to hERG and strong late sodium block, also led to such changes. However, verapamil, which leads to strong calcium and hERG channel block, did not cause T-wave morphology changes. The authors concluded that "a combined approach of assessing multiple ion channels, along with ECG intervals and T wave morphology, may provide the greatest insight into drug-ion channel interactions and torsade de pointes risk" (Vicente et al. 2015).

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Chapter 8

QTc Exposure–Response Modeling as a Primary Methodology for Proarrhythmic Cardiac Safety Assessments

The modifications of the proarrhythmic cardiac safety paradigm discussed in this chapter facilitate a move away from an environment in which a dedicated TQT study is conducted in later phases of clinical development towards one in which intensive ECG evaluation is conducted in the early phase of drug development during first-in-human studies.

8.1 Introduction

As has been noted several times, the third revision to the ICH E14 "Questions & Answers" document (ICH E14 Q&A R3) was released in December 2015. While QTc-concentration relationship analysis had assisted regulatory decision-making on a case-by-case basis for several years by that time (Garnett et al. 2008; Zhang et al. 2015), the release of ICH E14 Q&A R3 was a milestone in the domain of proarrhythmic cardiac safety. Its release validated widespread acknowledgment of the benefits of this methodology and created an alternative primary methodology for the evaluation of a drug's clinical QTc prolongation liability that can be employed much earlier in its clinical development program. Events occurring in the last few years leading to ICH E14 Q&A R3's release, which we collectively refer to as the Early QTc Assessment Initiative, are described in this chapter by discussing several publications that preceded its release: ICH E14 Q&A R3 itself is then addressed in Sect. 8.7.

8.2 Advantages of Exposure–Response Modeling as a Primary Methodology in Clinical Proarrhythmic Cardiac Safety Assessment

Exposure–response modeling, which is already regularly employed in other aspects of drug development (e.g., modeling the impact of drug–drug interactions and other intrinsic and extrinsic factors that can impact exposure, evaluating new

J.R. Turner et al., *Cardiovascular Safety in Drug Development and Therapeutic Use*, DOI 10.1007/978-3-319-40347-2_8

formulations), allows data to be analyzed across multiple cohorts and potentially multiple studies, in a single model. This is an important feature of the methodology since most Phase I studies use small cohorts for a given dose level and pool placebo data across cohorts (Bloomfield 2015). As an example, consider a sponsor who wishes to examine whether any of three doses of a drug, Dose A, Dose B, and Dose C, have an effect on QTc. Three cohorts of eight participants might be selected, one for each dose. In each case, a 3:1 randomization ratio would be employed to randomize six participants to the drug and two to placebo. This ratio maintains randomization while also permitting drug-related QTc data to be gathered from 75 % of those participating in the trial. Once all participants have completed the trial, six will have received each dose, and six will have received placebo. Exposure–response modeling using all the data collected would then permit estimation of the relationship between drug exposure and its effect (if any) on QTc over a wide range of concentrations.

This approach contrasts with the methodology employed by the TQT study in which attention falls on a specific set of time points for two specific doses, the proposed therapeutic dose and the chosen supratherapeutic dose. The intersection–union test treats dose and time points as independent categorical variables, ignoring the influence of drug concentration per se. This is an anomaly from the perspective of biological plausibility since most drugs prolong QTc as a function of plasma concentration. While the issues of multiplicity arising from evaluating QTc at every time point for both doses are appropriately addressed by the methodology underpinning the intersection–union test (as discussed in Chap. 5), it nonetheless can yield a bias towards false-positive results since it ignores reductions in QTc: in contrast, exposure–response modeling avoids such bias (Bloomfield 2015).

Exposure–response modeling also has additional advantages. Early-phase single ascending dose (SAD) and multiple-ascending dose (MAD) studies often explore the highest concentrations ever tested in humans. Over the last few years, some large pharmaceutical companies have started collecting robust QTc data in SAD and MAD studies by incorporating the elements of rigorous ECG collection and analysis utilized in TQT studies. To date, for the companies that have done so, this strategy has facilitated early but somewhat idiosyncratic internal decision-making regarding the viability of continuing with a drug's development program: some sponsors have likely terminated what could have been useful drugs with acceptable benefit–risk balances at the first hint of QTc liability. A formalized approach to rigorous early QTc assessment via the collection of robust QTc data and the employment of prespecified exposure–response models detailed in statistical analysis plans has the potential to provide useful information as early in a clinical development program as possible and hence facilitate a more structured, rational, and consistent approach to early go/no-go decision-making (Turner et al. 2015). While this approach requires collecting high-quality ECGs alongside pharmacokinetic sampling in one or more Phase I studies, the ability to extract ECGs from digital 24-h ECG recordings makes this feasible in most Phase I studies (Bloomfield 2015).

8.3 Discussions of Exposure–Response Modeling in the Second Revision of the ICH E14 "Questions & Answers" Document

Now that ICH E14 Q&A R3 has been released, the previous versions of this document are not posted on the ICH web site per se. However, the respective questions asked and answered in the original document and each of the three revisions can be identified within ICH E14 Q&A R3 by looking at the "Date of Approval" column for each question and associated answer:

- Questions and answers in the original document are identified by the date June 2008.
- Those in the first revision are identified by the date April 2012.
- Those in the second revision (ICH E14 Q&A R2) are identified by the date March 2014.
- Those in ICH E14 Q&A R3 are identified by the date December 2015.

One of the questions in ICH E14 Q&A R2 addressed the topic of exposure–response modeling. The relevant questions can be paraphrased as follows:

> The 2005 ICH E14 Guideline states that analysis of the relationship between drug concentration and QT/QTc interval changes is under active investigation. Has this investigation yielded a reasonable approach to concentration-response modeling during drug development? How can exposure–response modeling guide the interpretation of QTc data?

The answer presented can be paraphrased as follows:

> Exposure-response modeling can be an important component of a 'totality of evidence' assessment of the risk of QTc prolongation. It can be evaluated in early-phase studies and as part of the conventional study of QTc prolongation, and may help inform further evaluation. There are many different types of models for the analysis of concentration-response data, including descriptive pharmacodynamic (PD) models and empirical models that link pharmacokinetic (PK) models (dose-concentration-response) with PD models.
>
> An understanding of the exposure-response relationship can help predict the QTc effects of doses, dosing regimens, routes of administration, or formulations that were not studied directly. Interpolation within the range of concentrations studied is considered more reliable than extrapolation above the range.
>
> If the results for the study drug are ambiguous (e.g., QTc prolongation at lower dose but no prolongation at higher dose, or QTc prolongation at a single isolated time point), exposure-response analysis can help interpret the data.
>
> Careful replicate ECG collection with concurrent plasma drug concentrations measured in SAD and MAD studies provide a unique opportunity to evaluate potential drug-induced QTc effects over a broad range of doses and concentrations that might not be evaluated again during the drug development process. Pooling QTc and drug concentration data across doses, time, participants, and studies can yield large data sets to which PK-PD models can be applied to predict concentrations at which QTc prolongation could be clinically relevant. Exposure-response modeling applied on early clinical QTc data from healthy volunteers seems promising in terms of enhancing our confidence to characterize QTc prolongation.

Bloomfield (2015) commented upon the language used there, specifically that exposure–response modeling "seems promising." Using the abbreviation ER for exposure–response modeling, he noted that "the ICH E14 working group was unable to agree on specific guidance on how ER modeling could be used for regulatory decision making in lieu of a TQT study. A key gap identified was the lack of data available to the working group to inform the relationship between the traditional endpoints used in a TQT study and ER modeling."

See Shah and colleagues (2015) for additional commentary on ICH E14 Q&A R2.

8.4 An Illuminating Retrospective Study of QTc Exposure–Response Modeling

Zhang and colleagues provided insights regarding the numbers and types of studies evaluating QTc prolongation that were reported to the FDA between July 2006 and December 31, 2012 (Zhang et al. 2015). These studies were reviewed by their QT Interdisciplinary Review Team (QT-IRT), which was formed in 2006. The QT-IRT is responsible for reviewing study protocols and completed study reports addressing QTc liability assessment, including both TQT studies and non-TQT studies addressing this issue in the most feasible manner possible. Membership of the QT-IRT includes statisticians, clinical pharmacologists, medical officers, projects managers, and data managers. According to the intended indication for their candidate drug, sponsors submit QTc-related proposals and study reports to the appropriate therapeutic review division within FDA. The review division then forwards the document to the QT-IRT. Members review each document and give what is considered nonbinding advice to the review division. The division takes the QT-IRT's comments and recommendations into consideration when forming its response to the sponsor and communicates the response directly to the sponsor (Turner and Durham 2009).

During the six-and-a-half-year time window reported in Zhang and colleagues' paper, the QT-IRT reviewed nearly 1,500 QT-related documents, including protocols, meeting packages, and study reports. The total number of study reports was 277. Of these, 229 were TQT studies and 48 were non-TQT studies, studies that did not conform precisely to TQT study requirements but were nonetheless good faith attempts to assess QTc prolongation liability to the greatest degree possible in their particular circumstances.

The authors also presented the rationale for, and the results of, a retrospective investigation comparing TQT-like "negative" and "positive" designations for a large subset of these studies with the results of QTc-concentration relationship analysis using data from each respective study. From the 277 unique studies identified, 53 were excluded since pharmacokinetic information was missing, and one was excluded because of a clear case of hysteresis. Of the 223 studies therefore included in their analysis, 204 were TQT studies and 19 were non-TQT studies. Of the TQT

Table 8.1 Results from the Zhang et al. analysis by study type

Study type	Sensitivity and specificity
All studies ($N=223$)	86 % and 92 %
All TQT studies (204)	86 % and 95 %
Crossover design TQT studies ($N=141$)	88 % and 96 %
Parallel design TQT studies ($N=63$)	82 % and 93 %
Non-TQT studies ($N=19$)	86 % and 83 %

studies, 141 employed a crossover design, and 63 employed a parallel design. The two overall findings were as follows (Zhang et al. 2015):

- In 86 % of the cases where exposure–response analysis showed that the slope was not positive, i.e., there was no evidence of a relationship between drug concentration and QTc, the corresponding QT study had been designated as negative. This equates to a sensitivity of 86 %.
- In 92 % of the cases where exposure–response analysis revealed a positive slope, indicating a relationship between drug concentration and QTc, the corresponding QT study had been designated as positive. This equates to a specificity of 92 %.

In the present context, sensitivity measures the proportion of actual negative studies that are correctly identified as not demonstrating a QT-concentration relationship, and specificity measures the proportion of actual positive studies that are correctly identified as demonstrating a QT-concentration relationship. For completeness, Table 8.1 presents results for analyses conducted by type of study.

Following appropriate discussion of the study's limitations, the authors concluded that results from a QTc-concentration relationship analysis and those from the traditional ECH E14 analysis appear to be "strongly concordant" as long as the data collected and used in the QTc-concentration relationship analyses are of the same quality as those collected and used in ICH E14-guided analyses.

8.5 Prospective Evaluation of Exposure–Response Modeling: The IQ/CSRC Study

While retrospective analyses can certainly be very informative, prospective studies are typically awarded more gravitas. In 2013, a collaboration between the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ) (IQ web site 2015) and the CSRC was initiated to design and conduct a clinical trial in healthy participants to investigate in a prospective manner whether or not it might be possible to replace the TQT study by rigorous ECG monitoring and exposure–response modeling of data generated from SAD studies or at least to provide an alternate to the TQT study. The design of the IQ/CSRC study was published in 2014 (Darpo et al. 2014a) and the results were published in 2015 (Darpo et al. 2015a).

8.5.1 Design of the IQ/CSRC Prospective Study

The IQ/CSRC Prospective Clinical Phase 1 Study was a three-period, blinded, randomized, placebo-controlled study in 20 healthy participants conducted in a design similar to a Phase I SAD study, with the primary objective being to estimate the effect of the drugs on the QTc interval using exposure–response analysis. Six marketed drugs with well-characterized QT effects were selected for the evaluation, including five "QT-positive" drugs and one "QT-negative" drug. The QT-positive drugs, known to prolong the QT interval, were ondansetron, quinine, dolasetron, moxifloxacin, and dofetilide: the QT-negative drug, which is not associated with QT interval prolongation, was levocetirizine.

The QT-positive drugs were chosen after discussions with FDA. Selection criteria included a drug's toxicity profile (i.e., did it allow ethical administration of the drug to healthy participants?), lack of a substantial heart rate effect, and its degree of QTc prolongation. A lower dose administered on Day 1 was recommended by the FDA and was meant to achieve a mean placebo-corrected, change-from-baseline QTc (ΔΔQTc) of 9–12 msec. A higher dose, expected to result in ΔΔQTc of around 15–20 msec, was administered on Day 2. The higher dose was chosen to mimic a typical SAD study. In addition to similarity with a SAD design, the higher dose was intended to increase the precision of the slope of the estimated exposure–response model when data from the two dose levels were pooled. ECG recording, processing, and analysis were performed using rigorous methods as traditionally employed in TQT studies.

It was agreed ahead of time that if the results of the study were to show a positive QT-prolonging effect (upper bound of QTc change from baseline ≥10 ms at mean C_{max}) by exposure–response modeling for all five QT-positive drugs, and additionally excluded a QTc effect for the negative control drug levocetirizine, it would be deemed to have met its objective successfully (Darpo et al. 2014a, b).

The 20 healthy participants were randomized to a three-period crossover study design, where they received three of the six study drugs or placebo in an incomplete block design that resulted in each study drug being administered to nine participants and placebo being administered to six participants in separate periods.

8.5.2 Results of the IQ/CSRC Prospective Study

Results from the study showed that the upper bound of the 90 % confidence interval (CI) of the mean predicted placebo-adjusted QTc change from baseline at geometric C_{max} with all five QT-positive drugs exceeded 10 msec and that the slope of the exposure–response model was positive for all of these five drugs. In contrast, the upper bound for levocetirizine was less than 10 msec even when a single dose comprising six times the therapeutic dose was administered.

Using data from nine participants in each group treated with the study drug and six participants receiving placebo, the means (90 % CI) of the predicted ΔΔQTcF at

geometric $_{C\max}$ were as follows: 9.5 msec (7.2, 13.5) for ondansetron, 9.8 msec (6.7, 17.3) for quinine, 6.8 msec (3.4, 11.6) for dolasetron, 11.7 msec (10.6, 17.9) for moxifloxacin, 11.3 msec (6.1, 14.6) for dofetilide, and 2.0 msec (−2.6, 6.0) for levocetirizine.

While two participants received placebo in a crossover design in this study, first-in-human studies usually do not involve a crossover placebo period. After excluding these two participants, results for seven participants who had received the study drug or placebo in a parallel design were similar.

8.6 Concerns Expressed Following the Publication of the Results of the IQ/CSRC Study

While the IQ/CSRC Prospective Study certainly served as proof of concept, it had limitations and left some questions unaddressed (Turner et al. 2015). Some of these were discussed by Strnadova at the November 2014 DIA China Drug-Induced Cardiovascular Toxicity Workshop (Strnadova 2014):

1. Clinically relevant plasma concentrations of the drug and its metabolites are usually not known in early-phase clinical development.
2. Choice of ECG time points is limited by the lack of knowledge of the pharmacokinetics of the parent drug and metabolites.
3. SAD studies may be too short to detect delayed effects.
4. There is a need to demonstrate retrospectively that relevant concentrations and time points were studied.
5. The absence of a positive control to verify assay sensitivity in the proposed early-phase QT studies raises concerns about the risk of false negatives, i.e., the study excludes a QT effect for a drug that truly has one.
6. Exposure–response modeling is not standardized and the results can be operator and model dependent.
7. The utility of this approach using challenging compounds remains to be evaluated. This includes drugs with prominent effects on heart rate, slow elimination, poor tolerability, and drugs that affect QT by mechanisms other than hERG channel blockade.
8. Drugs associated with long half-lives (the parent drug or active metabolites) may need to be studied in MAD studies. The IQ/CSRC study did not address the design or analysis required in MAD studies.

It should also be noted that, in the IQ/CSRC study, drug doses were selected such that the lower dose was chosen with the intent of producing a mean ΔΔQTcF of 9–12 msec, and the higher dose was chosen with the intent of producing a mean ΔΔQTcF of 15–20 msec. TQT studies based on the ICH E14 traditional (i.e., by-time point) approach are designed to detect a mean ΔΔQTc of about 5 msec, with the 90 % upper bound of a two-sided confidence interval >10 msec. This magnitude of drug-induced QT effect is much lower than the expected and the observed QT

effect with the positive drugs in the IQ/CSRC study. Therefore, while the IQ/CSRC study does show that exposure–response modeling holds promise, at the time of writing this chapter, it is not known definitively whether the sample size traditionally employed in SAD and MAD studies is large enough to detect an effect size equivalent to that defined in ICH E14.

8.7 Details of ICH E14 Q&A R3

ICH E14 Q&A R3 (ICH E14 Implementation Working Group, 2015) contains one new section, numbered 5.1, that addresses exposure–response modeling of QTc data. The following text appears in the "Questions" column:

> The ICH E14 Guideline states (in Section 3, page 12) that analysis of the relationship between drug concentration and QT/QTc interval changes is under active investigation. Has this investigation yielded a reasonable approach to concentration-response modeling during drug development? How can assessment of the concentration-response relationship guide the interpretation of QTc data?

Given the importance of the information in the "Answers" column, it is reproduced here in full:

> Concentration-response analysis, in which all available data across all doses are used to characterize the potential for a drug to influence QTc, can serve as an alternative to the by-timepoint analysis or intersection-union test as the primary basis for decisions to classify the risk of a drug. In either case this result is an important component of the totality of evidence assessment of the risk of QT prolongation. The overall assessment of risk of QT prolongation includes nonclinical data, the time course of QT prolongation, the magnitude of QT prolongation, categorical analyses of outliers, and certain adverse events in patients that can signal potential proarrhythmic effects.
>
> There are many different types of models for the analysis of concentration-response data, including descriptive pharmacodynamic (PD) models (e.g., linear or Emax models), or empirical models that link pharmacokinetic (PK) models (dose-concentration-response) with PD models. It is recognized that concentration-response analyses of the same data using models with different underlying assumptions can generate discordant results. Therefore, it is important that the modeling methods and assumptions, criteria for model selection, rationale for model components, and potential for pooling of data across studies be specified prior to analysis to limit bias. Prospective specification of model characteristics (e.g., structural model, objective criteria, goodness of fit) based on knowledge of the pharmacology is recommended whenever possible. On occasion, the QT effect is not a direct function of plasma concentration. For example, drugs that cause QT prolongation as a result of changes in protein synthesis or trafficking or drugs with accumulation into myocardial tissues might demonstrate hysteresis. Testing for model assumptions, hysteresis (a plot of data by-time point and a hysteresis loop plot), and goodness of fit should be documented.

Concentration–response analysis can be challenging when more than one molecular entity—multiple drugs or parent plus metabolites—contributes to the QTc effect.

8.7.1 Important Considerations

Concentration–response data need not come from a dedicated QT study, nor even a single study, but there are several new and important considerations.

1. Data can be acquired from first-in-human studies, multiple-ascending dose studies, or other studies. Additional data would be useful to ensure information on exposure well above the exposure at the maximum therapeutic dose, to cover the impact of accumulation with repeated dosing, drug–drug and drug–food interactions, organ dysfunction, or genetically impaired metabolism. It is anticipated that one would collect new data to add to previous data, if appropriate, rather than using new data for independent analyses.
2. Efficient concentration–response analysis using data acquired in studies with other purposes requires as much quality control as is needed for a dedicated study. This includes robust, high-quality electrocardiogram (ECG) recording and analysis sufficient to support a valid assay for ECG intervals.
3. If there is an intention to pool data from multiple studies, it is important to test for heterogeneity.
4. If there are data characterizing the response at a sufficiently high multiple of the clinically relevant exposure (see E14 Sect. 2.2.2), a separate positive control would not be necessary.

8.7.2 Decision-Making

Both the intersection–union test and the concentration–response analysis can estimate the maximum effect of a drug treatment on the QTc interval, but they are not used to test the same hypothesis. As mentioned above, inspection of the time course of QT prolongation is important. However, hypothesis testing based on a by-time point analysis (intersection–union test or point estimate and confidence intervals) is inappropriate in studies designed for a concentration–response analysis, if not powered to assess the magnitude of QT prolongation for each time point. When using a concentration–response analysis as the primary basis for decisions to classify the risk of a drug, the upper bound of the two-sided 90 % confidence interval for the QTc effect of a drug treatment as estimated by exposure–response analysis should be <10 ms at the highest clinically relevant exposure to conclude that an expanded ECG safety evaluation during later stages of drug development is not needed.

8.7.3 Other Uses

In addition to serving as the basis for regulatory decision-making, concentration–response analysis has established its utility in several settings:

8.7.3.1 Providing Insight into Regimens Not Studied Directly

An understanding of the concentration–response relationship can help predict the QT effects of doses, dosing regimens, routes of administration, or formulations that were not studied directly. Interpolation within the range of concentrations studied is more reliable than extrapolation above the range.

8.7.3.2 Predicting QTc Effects of Intrinsic and Extrinsic Factors that Affect PK

Understanding the concentration–response relationship can help predict the effects of intrinsic (e.g., cytochrome P450 isoenzyme status) or extrinsic (e.g., drug–drug PK interactions) factors, possibly affecting inclusion criteria or dosing adjustments in later phase studies.

8.7.4 Comparison of Previously Noted Concerns with the Text of ICH E14 Q&A R3

Section 8.6 listed some concerns expressed following the publication of the results of the IQ/CSRC study. The concerns discussed were expressed before the release of ICH E14 Q&A R3, and so it is now appropriate to examine the degree to which ICH E14 Q&A R3 assuaged these concerns.

ICH E14 Q&A R3 emphasizes that concentration–response data need not come from a single study and that data from multiple studies can be used to ensure that exposures seen on accumulation with repeated dosing, or with drug–drug interactions, impaired metabolism, or increased excretory capacity, are accounted for. It recommends that aspects related to the pooling of data across studies and the modeling approach to be employed be specified a priori in the study's statistical analysis plan to limit bias. It is implied that using rigorous ECG recording and analysis to achieve low data variability (i.e., utilizing investigational sites with the same level of strict experimental control and utilizing the same technology and methods that have been used in TQT studies) and evaluating QTc response at multiples of the intended therapeutic dose to cover worst-case scenarios adequately would provide a high level of confidence in the absence of a positive effect and obviate the need for a positive control. This is supported by simulation studies performed on TQT data that have shown a low risk of false-negative results of around 5% (Darpo et al. 2015b). However, until more experience is gained, it may be reasonable to consider alternatives such as quality metrics, e.g., heart rate stability within time points or variability of the QT interval, as was done in the study reported by Nelson and colleagues (2015).

8.8 Anticipating Many Discussions of ICH E14 Q&A R3

At the time of writing this chapter, ICH E14 Q&A R3 has only recently been released. As with other documents released by ICH, there will likely be much discussion of individuals' and organizations' interpretation of its content at professional meetings and in the literature. When this book becomes available, readers are encouraged to look for articles published since this chapter's Further Reading list was finalized early in 2016. That said, we will share some thoughts at this point in time.

If a rigorous Phase I study were to be designed to provide all information needed to decide whether a waiver from a TQT study should be issued, some of the elements in the design and analysis would include the following:

- While it would be important to perform ECG recording with the same rigor as in a TQT study, ECGs would constitute only one of several safety parameters.
- Conventional ECGs would have to be replaced by high-resolution 12-lead Holter ECG recordings.
- Issues pertaining to diurnal changes in QTc would become important. There are considerable diurnal changes in the QTc interval, and it is important to differentiate these from true drug-induced changes. Moreover, diurnal changes could vary from participant to participant. In TQT studies, pre-dose ECGs recorded on the day of dosing are used as baseline in crossover studies where the same participant received the study drug as well as placebo. On the other hand, in parallel design studies, ECGs recorded on "Day 1" at the same time points as the post-dose ECGs are considered as time-matched baseline values for each individual participant. Early-phase studies typically have a parallel design, but whether "Day 1" baseline ECGs will be required to adjust for diurnal changes, or whether statistical modeling of diurnal changes would adequately replace the need for a "Day 1" recording, is not currently clear.
- In TQT studies, the use of a positive control served as a quality control measure that confirmed assay sensitivity. In early-phase studies, where a positive control is not traditionally used, other quality assurance measures would have to be identified. Some of these could be between- and within-participant variability in QTc and heart rate, but acceptable cut-off values have not yet been defined. Alternatively, adding a small subgroup of 6–10 participants receiving a positive control may be an easier approach.
- In data analysis, it would be important to test first for the presence of hysteresis between the drug concentration and the QTc effect. Darpo and colleagues (2015a) compared the T_{max} of the drug concentration with the T_{max} of the QT effect of the drug and proposed that if there was a difference of more than 1 h between the two- and the one-sided one-sample Wilcoxon test for the difference between maximum ΔΔQTcF and the value of ΔΔQTcF at T_{max} that was formally significant at the 1 % level, this would suggest presence of hysteresis. If hysteresis was seen, an effect compartment pharmacokinetic model would be needed.

- If the slope of the concentration-ΔΔQTcF relationship were to be positive, but the upper bound of estimated ΔΔQTcF at mean C_{max} of the therapeutic dose was <10 msec, at what multiple of the therapeutic dose, or at what multiple of mean C_{max} of the therapeutic dose, would one consider the drug to be safe or unsafe?

These considerations demonstrate that there are many complex issues pertaining to the design and statistical analysis of early-phase studies permitting a formal assessment of the QT liability of a new drug. Since published data addressing these considerations is currently limited, it may be a while before widely acceptable evidence-based guidelines will be formulated.

8.8.1 A Recently Reported Study of Interest

Of relevance to the discussions just mentioned is a study recently reported by Yu and colleagues (Yu et al. 2016). The overall study included both a Phase I dose escalation, placebo-controlled study and a TQT study for mipomersen. The Phase I study revealed no positive correlation between QTc and pharmacokinetic exposure across a wide dose range tested. The TQT yielded a "negative" finding, with upper bounds of two-sided 90 % confidence intervals well below 10 msec at both therapeutic and supratherapeutic doses. The authors concluded that the overall study results supported the proposal that "QT assessment can be made in a Phase I dose escalation study" and that a TQT study may not be necessary "if the Phase I dose escalation study showed a negative QT effect."

8.9 A Provocative Consideration?

Throughout this book's discussions, we have endeavored to provide factual descriptions of issues covered without accompanying personal interpretations. At this point, we have given ourselves a little latitude to consider a potential outcome of regulatory acceptance of QTc exposure–response modeling.

One is reminded at this point of television shows presenting fictitious but presumably reasonably accurate depictions of the consequences of a prosecuting attorney being found guilty (or perhaps even simply being accused of being guilty) of inappropriate conduct during the successful prosecution of a defendant. Every previous successful prosecution of other defendants by the same prosecuting attorney will likely be called into question by defense attorneys keen to overturn the respective verdicts.

Consider, therefore, the paper published by Barbour and colleagues discussing the results of a TQT study for losmapimod (Barbour et al. 2015). Losmapimod is "a

novel, oral p38 mitogen-activated protein kinase (MAPK) inhibitor that targets MAPKs activated in macrophages, myocardium, and endothelial cells that occur as a part of global coronary vascular inflammation following plaque rupture" (Kragholm et al. 2015). The TQT study resulted in a positive finding. However, the authors commented as follows (Barbour et al. 2015):

> Simulations using the concentration-effect model established for QTcF vs. losmapimod concentration at concentrations 4× the maximum concentration of the therapeutic dose did not exceed the regulatory thresholds of concern of 5 milliseconds for the mean (4.57 milliseconds) and 10 milliseconds for the upper bound of the 90% CI (90%CI 2.88, 6.10). Modeling demonstrated that the discrepant results may have been due to a baseline shift after repeat dosing and baseline differences between the treatments. Considering the results of the concentration-effect modeling, previous losmapimod data, and the high false-positive rate associated with the ICH E14 statistical analysis, the statistical analysis was likely a false-positive.

In October 2015, the drug's sponsor announced that an interim analysis of data from an initial cohort participating in LATITUDE-TIMI 60 (O'Donoghue et al. 2015), a Phase III study in which the primary efficacy endpoint was a composite measure of major adverse cardiovascular events (time to first occurrence of cardiovascular death, myocardial infarction, or severe recurrent ischemia requiring urgent coronary artery revascularization), did not support efficacy against the primary endpoint. The sponsor noted that these results "did not support investment" in the larger, second part of the trial as it was originally designed, and that they would "assess these findings over the next few months to evaluate all options for future development" (LATITUDE-TIMI 60 Press Release 2015). As of writing this chapter, the significance of the "discrepancy" between a positive TQT study result and the concentration-effect modeling data is not clear.

However, imagine a scenario in which a drug has received marketing approval by a given regulatory agency and its label in the agency's jurisdiction contains warning information about the potential for QT interval prolongation that is based on the results of a TQT study. Imagine further that the drug's sponsor believes that the results from the TQT study were a false-positive "identification" of a QT prolongation liability and believes that exposure–response modeling would provide evidence exonerating the drug from QT prolongation liability. Given that ICH E14 Q&A R3 now states that exposure–response modeling can be used for such exoneration (although the intent is likely to refer to a sponsor's first choice of methodology), what would happen if the sponsor conducted such modeling and submitted data exonerating the drug from QT liability to the regulatory agency? Might the agency then reverse their labeling decision based on the TQT study data? And if so, would such an occurrence lead to a torrent of similar requests from sponsors of other drugs with QT prolongation liability warnings in their labels? Again, if so, might the demand on the regulators' time interfere with their ability to review cardiac safety data for new drugs being considered for marketing approval? We do not presume to have the answers to these questions at this point: time will tell.

8.10 Concluding Comments

Although the original ICH E14 response a decade ago to the issue of QTc liability and drug-induced *torsades* was, in retrospect, arguably over-engineered and resource intensive, it has worked well in preventing marketing withdrawals. However, it has also the unintended consequence of higher attrition in the development programs of potentially useful drugs. The modifications to the proarrhythmic cardiac safety paradigm discussed in this chapter build on its success while addressing some of the limitations of the strategy of proarrhythmic risk assessment employed circa 2005–2015. These modifications are triggering a move away from an environment in which a dedicated TQT study is conducted in later phases of clinical development and towards an environment in which intensive ECG evaluation is conducted in the early phase of drug development using existing first-in-human studies.

Zhang and colleagues (2015) observed that the employment of rigorous exposure–response modeling might "avoid an unnecessary TQT study in many cases." They also provided a word of caution: "However, like most analytic methods, there are still some grey areas in which this analysis alone cannot determine the potential QT liability of the drug." Whichever assessment methodology is used in a given case, ECG evaluation will continue to be an important tool in the field of proarrhythmic cardiac safety.

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Chapter 9

The Comprehensive In Vitro Proarrhythmia Assay Initiative

These new strategies have the potential to improve sensitivity and specificity in the early detection of genuine cardiotoxicity risks, thereby reducing the likelihood of mistakenly discarding viable drug candidates and speeding the progression of worthy drugs into clinical trials (Gintant et al. 2016).

9.1 Introduction

This chapter discusses the Comprehensive In Vitro Proarrhythmia Assay (CiPA) initiative, an integrated set of investigations that may lead to modifications of the nonclinical proarrhythmic cardiac safety regulatory landscape. Underlying this initiative is the fact that drug-induced I_{Kr} reduction and QTc interval prolongation are far from ideal surrogates for actual proarrhythmic risk, the true concern in the domain of proarrhythmic cardiac safety. The link between drug-induced QTc prolongation and the rare (but potentially lethal) arrhythmia *torsades* appears to be multifaceted, and occurrence of drug-induced *torsades* typically requires multiple contributing factors to be present simultaneously. Some of these clinical risk factors include female sex, structural heart disease, metabolic and electrolyte abnormalities, bradycardia and pauses, increased concentrations of "culprit" drugs, and inherited syndromes causing QT prolongation (Vlachos et al. 2016). Sager and colleagues (2014) therefore observed that, given our advancing knowledge and understanding on multiple fronts, it is incumbent upon us to provide a more comprehensive evaluation of actual proarrhythmic risk. These advances are evident in our knowledge of mechanisms responsible for *torsades*, our ability to evaluate drug effects on human cardiac ion channels, successes in in silico modeling of human ventricular electrical activity, and the evolving employment of isolated human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs).

The CiPA paradigm is comprised of three fundamental components: a two-component core in vitro strategy assessing effects on isolated cardiac currents and integrated drug responses from hiPSC-CMs and in silico reconstructions of cellular electrophysiological activity. An additional step is the definition of the proarrhythmic risk of a select group of drugs used clinically, thereby defining a "gold standard"

J.R. Turner et al., *Cardiovascular Safety in Drug Development and Therapeutic Use*, DOI 10.1007/978-3-319-40347-2_9

for comparison of nonclinical and clinical findings. Organized as a public–private collaboration, CiPA represents a mechanistic-based set of investigations that will provide a better understanding of a drug's proarrhythmic liability. The initiative is being driven by an international consortium comprising multiple collaborators including the FDA, EMA, Health Canada, PMDA, CSRC, the Health and Environmental Sciences Institute (HESI), the Safety Pharmacology Society (SPS), Japan National Institute of Health Sciences, Japan iPS Cardiac Safety Assessment, academics, in silico modelers, and partners from contract research organizations, the pharmaceutical industry, stem cell providers, and medical device companies (Fermini et al. 2016).

The first major presentation and discussion of CiPA occurred at a July 2013 Think Tank Meeting sponsored by CSRC, HESI, and FDA: a report was provided by Sager and colleagues (2014). Following that meeting, workstreams were created to focus on various aspects of CiPA, with each workstream operating under the auspices of a collaborating organization. The Ion Channel Working Group was established by SPS, the In Silico Working Group operates under the direction of FDA, the Cardiac Myocyte Working Group is sponsored by HESI, and the Clinical Translation Working Group operates under joint direction from the CSRC and HESI. A subsequent Think Tank Meeting sponsored by FDA, CSRC, HESI, and SPS provided an update on their work in December 2014, and additional discussion has been presented by Fermini and colleagues (Fermini et al. 2016).

9.2 Advantages of the Proposed Paradigm

The CiPA paradigm addresses many of the concerns related to the traditional ICH S7B and ICH E14 approaches. Importantly, CiPA focuses on the assessment of potential ventricular proarrhythmia risk via a mechanistically robust set of input data rather than employment of the surrogates of I_{Kr} reduction and QTc prolongation. Drugs with increased proarrhythmic risk would be assessed for their potential to enhance vulnerability to disrupt repolarization rather than simply to delay repolarization. Moving the mainstay of the assessment of proarrhythmic risk away from later (clinical) drug development to earlier stages of drug discovery, hence permitting its deployment in candidate selection, will likely prevent the current common scenario that a small QTc prolongation signal seen in drug development constitutes uncertain risk that is to be avoided, resulting in the premature discontinuation of a compound that may have been therapeutically beneficial and had an acceptable benefit–risk balance.

A second advantage is that the CiPA paradigm is not dependent on dichotomous categorization, i.e., prolongation vs. no prolongation of QTc. A graduated risk scale that would permit improved benefit–risk assessments is envisioned. Some degree of proarrhythmic risk may be considered acceptable for some drugs addressing unmet medical needs, e.g., serious oncologic diseases and chronic, debilitating diseases, but not for other drugs such as those for allergic rhinitis. The vision for CiPA is a

nonbinary output in which novel compounds are given a proarrhythmic risk score predicated on a continuous scale that has been calibrated against a test set of clinical drugs spanning the range of proarrhythmic risk.

This paradigm also offers the facilitation of more informative package inserts at the time of a new drug's marketing approval and also the relabeling of those compounds that currently have QTc warnings and precautions but for which a true low proarrhythmic risk can now be identified.

9.3 Cardiac Ionic Currents of Particular Interest

Numerous overlapping ionic currents contribute to the determination of the morphology and duration of the ventricular action potential: those discussed in this chapter are summarized in Table 9.1.

While there are multiple repolarizing potassium currents, I_{Kr} has attracted particular attention in two contexts: the inherited channelopathy LQT2 (Bunch and Ackerman 2007; McBride et al. 2013; Smith et al. 2013) (recall discussions in Chap. 3) and drug-induced (acquired) QTc prolongation. In LQT2, an abnormal variant of the *hERG* gene produces hERG channels with decreased expression or function, leading to a decrease in repolarizing I_{Kr}. In the case of drug-induced hERG channel blockade, a small-molecule drug typically binds to the inner walls of the central pore of the channel and impedes I_{Kr}. Many noncardiac drugs block the hERG channel in preference to other cardiac potassium channels as a result of differences in its intracellular channel vestibule and pore structure, characteristics that have led to the channel being described as "an unusually promiscuous target among potassium

Table 9.1 Ionic currents and their influence on each phase of the action potential

Ionic current	Influence
$I_{Na[fast]}$	Rapid inward sodium current responsible for depolarization and rising phase of the action potential (phase 0),
I_{to}	Transient outward repolarizing current comprised of multiple overlapping outward repolarizing potassium currents (phase 1)
$I_{Na[late]}$	Late sodium (depolarizing) current governing the plateau phase of the action potential (phase 2)
I_{CaL}	L-type calcium (depolarizing) current governing the plateau phase of the action potential (phase 2)
I_{Ks}	Slow component of the delayed rectifier potassium current especially prominent in supporting repolarization (phase 3) with beta-adrenergic stimulation
I_{Kr}	Rapid component of the delayed rectifier potassium current responsible for the transition from plateau to terminal (phase 3) repolarization
I_{K1}	Inward rectifier potassium current (an outward repolarizing current) responsible for terminal repolarization of the action potential and sustaining the resting membrane potential of ventricular cardiomyocytes during diastole (phase 4)

channels" (Lagrutta et al. 2008). While the mechanism of action is different (inherited vs. acquired), hERG blockade therefore results in the same cascade of occurrences as does LQT2, i.e., a reduction of repolarizing I_{Kr} and delayed ventricular repolarization manifesting as QT prolongation. Given this commonality, drug-induced QT prolongation, like LQT2, is also of considerable clinical concern.

All other influences being kept equal, a drug-induced decrease in I_{Kr} will lead to a reduction in overall (net) repolarizing current. However, the relationships between the amount of hERG block, the extent of delayed repolarization/QT prolongation, and the proclivity and incidence of proarrhythmia/*torsades* are uncertain and likely dependent on the kinetics and extent of I_{Kr} block, block of other cardiac channels during repolarization (termed multi-channel block), and the underlying electrophysiologic substrate (which may be altered in the setting of cardiac disease). Two possibilities arise. The same drug molecule can affect one or more of the multiple other cardiac ion channels, thereby affecting multiple ionic currents to affect net outward current. Depending on the channels affected, as well as kinetics and extent of block, multi-channel block may effectively minimize or cancel out the decrease in repolarizing influence due to hERG channel block, leading to minimal (if any) proarrhythmic effects. Alternatively, decreases in both I_{Kr} and I_{Ks} could have additive/synergistic effects not appreciated by evaluating hERG channel block alone. This notion is embodied in the term repolarization reserve, which recognizes that both I_{Kr} and I_{Ks} define ventricular repolarization: with one current (e.g., I_{Ks}) already reduced, block of the second (I_{Kr}) will have greater effects on repolarization and potentially convey more proarrhythmic liability in the presence of reduced baseline repolarizing current. Malik (2016) commented on the term repolarization reserve as follows:

> It suggests that the interplay between different ion channels that maintain myocardial repolarization is to some extent redundant and that this redundancy offers mechanisms protecting against externally induced abnormalities including drug-induced anomalies. The susceptibility to arrhythmic consequences of drug-induced repolarization changes markedly increases when other pathological processes reduce this built-in protection.

Advances in the capabilities and adoption of higher-throughput automated voltage clamp patch platforms will facilitate more efficient characterization of drug effects on multiple cardiac currents (Dale et al. 2007; Castle et al. 2009; Ma et al. 2011; Farre and Fertig 2012; Di Veroli et al. 2013). Employing higher-throughput automated patch techniques will also provide sufficient sample size and statistical power to facilitate parameterization of subsequent in silico reconstruction efforts and to determine IC_{50} and other characteristics of block as deemed necessary to provide reliable, reproducible characterization of integrated electrophysiological effects.

9.4 Electrophysiological Principles Underlying CiPA

As previously noted, the relationships between the degree of hERG block, the extent of delayed repolarization/QT prolongation, and the proclivity and incidence of proarrhythmia/*torsades* are uncertain. Not all drugs that prolong QTc are

proarrhythmic; examples include ranolazine, phenobarbital, and tolterodine. Verapamil is a potent hERG current blocker, but it does not cause QTc prolongation (except possibly at very high intravenous exposures), likely as a result of its concomitant blockade of calcium current (Zhang et al. 1999). Amiodarone is an example of a drug that causes marked QTc prolongation (not infrequently to lengths >550 msec) and yet only very rarely causes *torsades*.

It is likely that drug effects on multiple cardiac currents, especially reductions of inward (depolarizing) calcium and sodium currents during the action potential plateau, provide protection from proarrhythmia when coupled with a decrease of I_{Kr}. The concept that block of non-hERG currents may mitigate proarrhythmic effects of hERG current block is not new: it has been known for some years that combining block of repolarizing potassium current with either sodium or calcium channel block may reduce or reverse early after-depolarization (EAD) formation (Bril et al. 1996; Martin et al. 2004), a topic discussed in the following section. A review of the potency of I_{Kr} block (relative to clinical exposures) and TQT study results for 39 drugs demonstrated the need for additional nonclinical assays addressing drug effects on other currents to assess more comprehensively the risk of QTc prolongation (Gintant 2011). More recently, a logistic-regression approach involving assessment of drug effects on three cardiac channels, Kv11.1 or hERG (I_{Kr}), fast sodium Nav1.5 ($I_{Na\ fast}$), and Cav1.2 (I_{CaL}), showed a significant reduction in false-positive and false-negative classifications for 55 drugs from multiple classes (32 torsadogenic and 23 non-torsadogenic drugs) as compared with predictions based on I_{Kr} block alone (Kramer et al. 2013).

These observations reinforce the need to consider drug effects on multiple cardiac currents when assessing proarrhythmic liabilities. Some companies are already screening multiple cardiac ion channels in drug discovery (Davies et al. 2012). The ionic current studies component of the CiPA paradigm would provide standardized, best practice assays to ensure valuable data sets that inform decisions regarding cardiac safety early in drug discovery, provide guidance on first-in-human studies, and generate valuable information for regulatory considerations.

9.4.1 Early After-Depolarizations

Early after-depolarizations (EADs) are slowly rising depolarizations that occur during the later phases of an action potential after the initial depolarization (termed the "triggering event") that inscribe a second depolarizing upstroke (hence the term "after-depolarization") that occurs prior to full repolarization (hence an "early" after-depolarization) (see Chang et al. 2012). A stylistic representation of an EAD can be seen as Figure 1B in an Open Access paper by Sager and colleagues (2014). If they are of sufficiently large amplitude and occur at specific times during repolarization, EADs can trigger single or multiple premature ventricular depolarizations that may propagate throughout the ventricles. In the setting of enhanced dispersion of repolarization (a phenomenon that can occur with nonuniform drug-induced

prolongation of repolarization in different regions of the ventricular myocardium), and sometimes coupled to rhythm disturbances, EAD-triggered responses may give rise to *torsades*. CiPA therefore focuses on cellular electrophysiological effects of drugs that modify repolarization to enable EADs. This focus is in line with generally increasing emphasis being placed on early EADs and the microenvironments that elicit and support their morphology and dynamics (Qu et al. 2013b).

Outward potassium current, mostly I_{Kr}, promotes repolarization and suppresses re-excitation during the plateau of each action potential until terminal repolarization ensues with the subsequent contribution of I_{K1}. When repolarization is impaired, EADs can arise, initiating triggered activity likely resulting from I_{CaL} "reactivation" or window current. The dynamic balance of inward vs. outward currents predisposes to triggered activity. Arrhythmias can only arise where net inward current during repolarization occurs, allowing the early activity of one part of the heart to affect activity in another part with a delay, which then eventually makes its way back to the first area with sufficient delay to set up a loop or reentrant circuit. Although the exact circumstances that give rise to the conduction loop are not well characterized, the vulnerability resulting from a drug's effects on various ion channels leading to triggered activity can be assessed with great precision using in silico reconstructions based on human ventricular activity (Sager et al. 2014).

9.5 CiPA's Core In Vitro Strategy

The core in vitro strategy focuses on the evaluation of drug effects on multiple isolated human cardiac currents via heterologous expression systems assessed electrically using voltage/patch clamp techniques. As we have seen, multiple currents define the cardiac action potential, and knowledge gleaned from inherited LQTS and drug-induced proarrhythmia convincingly demonstrate that repolarizing and depolarizing currents must both be considered to understand proarrhythmia. I_{Kr} represents only one of multiple potassium and sodium currents that, when differing from normal, are associated with long QT and proarrhythmia. Studies of acquired LQT syndromes and proarrhythmia demonstrate that fast inward sodium current and enhanced inward current ($I_{Na\text{-}Late}$ or reactivation of calcium current during the action potential plateau) are also involved in proarrhythmia. Thus, a more comprehensive in vitro set of ion current assays could conceivably explore I_{Kr}, I_{Ks}, and I_{K1}, as well as $I_{Na\text{-}Fast}$, $I_{Na\text{-}Late}$, and $I_{Ca\text{-}L}$ for drug effects. The specific currents to be evaluated to generate a sufficiently comprehensive and predictive data set are currently under discussion by various workstreams.

The use of voltage clamp studies for unbiased and standardized decision-making in arrhythmia evaluation will necessitate the development of consensus on best practices and/or standardization of protocols, positive/negative controls, and experimental conditions. This effort will reduce variability, allow comparisons across assays and laboratories, and generate movement towards more uniform data quality for purposes of decision-making, both by sponsors internally and by regulatory

agencies. As one example, multiple studies demonstrate that the potency of I_{Kr} blockade is, at least for some drugs, affected by the experimental temperature, i.e., room temperature vs. physiologic temperature (37°C). It is becoming clear that the potency of drugs that demonstrate prominent temperature-dependent effects is uncertain, necessitating an evaluation of hERG blocking potency at physiologic temperature.

Within CiPA, the potency of current block (based on IC_{50} values) relative to free drug plasma concentration will be a key component in evaluating a drug's proarrhythmic liability. Further characterization of the kinetics of block, e.g., including voltage, time, and concentration dependence, might be critical for some currents, likely including I_{Kr}: comparison of in silico studies incorporating conductance block models with those incorporating kinetics of drug block and unblock will guide future discussions (Di Veroli et al. 2013).

9.6 CiPA's In Silico Modeling Component

In silico models of cellular human ventricular activity are employed to integrate drug effects on multiple cardiac currents, providing reconstructions of cellular electrical activity. Electrophysiological models have been used since the pioneering work of Hodgkin and Huxley to reconstruct neuronal excitability of squid giant axons based on contributions of overlapping voltage- and time-dependent sodium and potassium currents (Hodgkin and Huxley 1952; Krouchev et al. 2015). In the CiPA paradigm, voltage clamp data describing a drug's effects on multiple ionic currents, based on the O'Hara–Rudy model (O'Hara et al. 2011), will describe effects on ventricular repolarization that are not easily understood from effects on any individual cardiac current.

It is envisioned that in silico reconstructions will provide information on two fronts: drug effects related to the ability to elicit EADs during Phase 3 repolarization based on measures of net current during repolarization and evaluation of the robustness of repolarization based on the ability of depolarizing currents applied during the action potential plateau to amplify delayed repolarization and EAD activity. A scoring system may be necessary to rank order proarrhythmic risk based on measures of repolarization instability calibrated against a training set of compounds affecting multiple cardiac ion channels that have been ranked according to clinical *torsades* risk. This continuous scoring system could then be used to rank order drug candidates' risk of *torsades* proarrhythmia in the context of therapeutic margins, e.g., therapeutic concentration and plasma protein binding.

In support of the use of integrative in silico models, a study by Mirams and colleagues (Mirams et al. 2011) employing in silico modeling to measure action potential prolongation demonstrated that evaluation of drug effects across three human ion channels (Kv11.1, Nav1.5, and Cav1.2) improved prediction of torsadogenic risk compared with evaluations based solely on hERG channel block. Numerous studies have described the general utility of in silico ventricular reconstructions in

evaluating overall delayed repolarization liabilities and/or proarrhythmic risk (Valentin and Hammond 2008; Fletcher et al. 2011; Mirams et al. 2011, 2012; Kramer et al. 2013; Beattie et al. 2013).

The best in silico cellular model(s) for reconstructions will have to be selected and then made available to users in a standardized format to provide meaningful ranking of proarrhythmia across different laboratories or, alternatively, be made widely available on a centralized cloud-based resource.

9.7 Effects on hiPSC-CMs

CiPA's third component is the evaluation of drug effects on the electrical activity of hiPSC-CMs. This approach yields a cell-based integrated electrophysiological drug response, providing a check on the adequacy of the voltage clamp data and in silico reconstructions of ventricular electrical activity: it is critical to ensure that drug effects not detected in voltage clamp-based ionic current assays and in silico models are detected and evaluated. Isolation and propagation of human-induced pluripotent stem cells and hiPSC-CMs has provided a useful source of cells for applications in drug discovery and cardiotoxicity screening (Mordwinkin et al. 2013).

Voltage clamp studies of hiPSC-CMs have demonstrated the presence of currents expected in adult ventricular myocytes (Ma et al. 2011; Hoekstra et al. 2012) and effects on repolarization consistent with human responses (Hoekstra et al. 2012; Peng et al. 2010). However, studies have shown that hiPSC-CMs demonstrate a relatively immature phenotype compared with adult human myocytes (Jonsson et al. 2012; Qu et al. 2013a). Despite these limitations, numerous studies have demonstrated their ability to detect responses consistent with clinical findings. Thus, while they represent a model system, human ventricular myocytes presently do not fully recapitulate the native adult ventricular myocyte in all functional aspects. Efforts are ongoing in multiple laboratories to provide more representative, or mature, ventricular myocytes. Once successful, fully mature hiPSC-CMs (expressing all the ionic currents with the same densities and characteristics as adult human ventricular myocytes) should replace most in vitro proarrhythmia testing approaches. Furthermore, it should also be possible to test evolving diseased ventricular myocyte models in vitro to evaluate drug effects on at-risk populations (the so-called disease in a dish studies).

A critical assessment of present practices and data yielded from hiPSC-CMs will be necessary in defining the most appropriate experimental methodologies and their limitations. As hiPSC-CMs represent a relatively new and rapidly evolving area of investigation, it is necessary to characterize these preparations more fully and build consensus on their ability to provide consistent data across laboratories and methods. As is the case for all new in vitro preparations, the selection of hiPSC-CMs and the experimental conditions in which they are employed will need to be rigorously defined to facilitate subsequent standardization for use in CiPA.

9.8 Updates from the CiPA Working Groups

Updates from each working group are provided in turn.

9.8.1 The Ion Channel Working Group

The Ion Channel Working Group utilizes the expertise and experience of its members in the fields of ion channel biophysics and pharmacology and in the translation from in vitro to in vivo models. The group is tasked with "bringing together expertise and resources required to deliver best practice recommendations for generating ion channel data needed for in silico human cardiac action potential reconstructions of proarrhythmic liabilities" (Fermini et al. 2016).

Since its launch in January 2014, this working group has focused on addressing several important questions related to best practices, including the following: Which ion channels are necessary to best support in silico action potential modeling? Which characteristics of drug block should be studied (e.g., IC_{50} determinations, kinetics of block and unblock, rate/use/voltage dependence of block)? What is required to deliver robust, reliable, and reproducible ion channel data in a high-throughput screening environment in support of in silico action potential reconstruction?

As a first step, the group distributed a survey to active members of SPS to collect frequency/type data on the commonly used ion channels in their laboratories to obtain qualitative information on their relevance to drug-induced cardiac safety concerns, with a specific focus on proarrhythmia. The survey was critical in identifying seven ionic currents that are routinely studied because of perceived safety concerns: I_{Kr}, I_{Ks}, I_{to}, I_{K1}, $I_{Ca,}$ $I_{Na[fast]}$, and $I_{Na[late]}$: these currents were described in Table 9.1. Consequently, protocols are being developed for each of these ionic currents, with the intent of gathering key data to be used for in silico action potential reconstructions.

The channels used for cardiac ionic current studies are typically human clones overexpressed in heterologous expression systems, typically human embryonic kidney (HEK) or Chinese hamster ovary (CHO) cells. While these models are useful, it is recognized that comparisons of the characteristics and drug sensitivities of these currents with currents expressed in native adult ventricular myocytes are lacking. This lack, however, is not considered a significant impediment. Therefore, experiments evaluating drug effects on ionic currents will focus on the following candidate human recombinant channels:

- Nav1.5 (through which the rapid I_{Na} current flows)
- Toxin-modified (ATX II) Nav1.5 ($I_{Na[late]}$)
- Cav1.2 (I_{CaL})
- Kv4.3 + KChIP2 (I_{to})
- hERG (I_{Kr})
- KCNQ1 + KCNE1 (I_{Ks})
- Kir2.1 (I_{K1})

Emphasis is first being placed on I_{Kr}, consistent with its prominent role in defining ventricular repolarization and the ability of many drugs to block this current. Currents will be studied individually using protocols that will assess potencies of block and kinetics that might prove critical in understanding a compound's potential proarrhythmic liability. Ultimately, only the most informative protocols will be retained (and then standardized) for the CiPA paradigm. It is therefore likely that the list of seven targeted channels just provided will narrow once their roles as proarrhythmic markers are, or are not, confirmed. It is also expected that this work will facilitate the establishment of best practices for the employment of automated patch systems in studies characterizing drug effects (Fermini et al. 2016).

9.8.2 The In Silico Working Group

The In Silico Working Group is responsible for "the development and validation of the best in silico model of human ventricular electrophysiology for the action potential reconstruction of drug effects on the individual ion channel, as determined by the work of the Ion Channel Working Group" (Fermini et al. 2016). It will do so by integrating results from that group's work on drug effects on individual ion currents. In silico modeling offers the potential "to provide integrative, cost-effective, and high-throughput solutions to predict drug-induced changes in action potential duration" (Fermini et al. 2016). While the O'Hara–Rudy model of the human ventricle was selected by leading in silico modelers in July 2013, further details of drug effects on current kinetics are being incorporated into the model. This model offers several advantages:

- It is open source (see the Rudy Laboratory research section of the web site http://rudylab.wustl.edu).
- All constants (extracellular ionic concentrations, cell geometry, ionic conductance) and all the initial conditions for state variables and scaling factors have been determined.
- It is fully validated with ionic data described for a human ventricular action potential model.

Initial testing of the model was conducted using robust estimates of IC_{50} values for block for each of the seven targeted channels for a subset of 12 drugs with well-characterized clinical risk profiles. Comparing these reconstructions with known clinical risk of proarrhythmia informs decisions on which candidate channels are essential within the CiPA paradigm and whether the model can be improved. Pilot simulation studies using the model and data for block of I_{Kr} current with dofetilide (a specific I_{Kr} blocking agent) suggest that, at least for I_{Kr}, block potency alone is not fully adequate for assessing a drug's ability to delay ventricular repolarization and/or induce EADs. Once the final set of targeted test channels and detailed blocking characteristics are determined, the most promising candidate risk metric(s) will be identified based on model performance and boundary conditions compared with clinical *torsades* risk for an independent set of 28 well-characterized drugs (Fermini et al. 2016).

9.8.3 The Myocyte Working Group

The role of hiPSC-CMs within CiPA is "to define best practice for experiments using human stem cell-derived cardiomyocytes in an effort to validate drug effects observed on ion channels, and/or *in silico* modeling, and to unmask effects that, for various reasons, were not revealed in either the ion channel or *in silico* work" (Fermini et al. 2016). hiPSC-CMs offer clear advantages compared with isolated primary human cardiac cells or cardiac tissue preparations, both in terms of availability and ease of use. However, multiple aspects of their biology and pharmacology still need to be determined with certainty.

While some preliminary studies have taken place, additional experiments and validation work need to be completed to more fully assess "the functional utility of human stem cell-derived myocytes for determining the proarrhythmic risk of established and future drugs" (Fermini et al. 2016). As with other work groups, this will entail standardized procedures and defining best practices.

9.8.4 The Clinical Translation Working Group

The Clinical Translation Working Group's members were chosen based on their clinical experience with drug-induced proarrhythmia and clinical ECG studies. This group has evaluated compounds associated with QTc prolongation and *torsades* proarrhythmia and selected a cohort of compounds for the development and testing of the in silico model and the stem cell experiments. The intent of the compound set is to provide a set of "gold standard" drugs that represent a varied spectrum of multiple electrophysiological mechanisms, including multi-channel blocking drugs. The ranking of compounds with regard to clinically demonstrated torsadogenic risk/occurrence was based on published reports, the FDA Adverse Events Reporting System database, other published data sources, and the opinion of expert clinical electrophysiologists. Compounds were grouped into three risk stratification categories: very low (i.e., no risk), intermediate, and high risk. Drugs classified into these proarrhythmia categories are presented in Table 9.2.

9.9 Challenges Remaining to Be Addressed

As Fermini and colleagues (Fermini et al. 2016) noted, while CiPA is an attractive proposal, it will require a significant amount of work and likely several years of testing before regulatory guidelines can be updated definitively. One strength is that technology currently available can perform the necessary ion channel work in a high-throughput environment, albeit most likely at ambient rather than physiological temperature. On the flip side of the coin, while recording of ionic currents from

Table 9.2 Compounds classified at various risk stratifications

Very low (no) risk	Intermediate risk	High risk
Diltiazem	Astemizole	Azimilide
Loratadine	Chlorpromazine	Bepridil
Metoprolol	Cisapride	Dofetilide
Mexiletine	Clarithromycin	Ibutilide
Nifedipine	Clozapine	Quinidine
Nitrendipine	Domperidone	Vandetanib
Ranolazine	Droperidol	Methadone
Tamoxifen	Ondansetron	D, l-sotalol
Verapamil	Pimozide	
	Risperidone	
	Terfenadine	

recombinant channels expressed in various cell lines offers considerable advantages compared with recording endogenous currents in human cardiac myocytes, the underlying properties of these channels may not fully recapitulate those of endogenous channels. Full validation of the ion channel assays for the chosen targets will require time, effort, and likely additional funding.

As of writing this chapter, the CiPA Steering Committee still has important issues to address. One example concerns the stage of nonclinical drug development at which the CiPA paradigm will be applied: will it be at the point of lead identification, lead optimization, or candidate drug selection? Providing answers to these questions that will be accepted by worldwide regulatory agencies will likely not happen for some time: as Fermini and colleagues concluded, CiPA is "an evolving initiative with evolving workflows that will require scientific, intellectual, and practical contributions from multiple parties and, in consequence, will require time to be successful" (Fermini et al. 2016).

9.10 Anticipating Many Discussions of CiPA in the Literature

Since work on various aspects of the CiPA paradigm is ongoing at the time of writing this chapter, the current text provides a snapshot in time of the evolution of a potential regulatory landscape. A detailed report was provided in February 2016 by Gintant and colleagues (2016). As for the previous chapter, readers are encouraged to search for articles published since this chapter's Further Reading list was finalized in March 2016.

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Part V
Additional Domains of Cardiovascular Safety

Chapter 10

Oncology Drug Therapy: Cardiotoxicity and the Discipline of Cardio-oncology

Treating physicians need to be thoroughly acquainted with the cardiotoxic effects of anti-cancer drugs so that they can diagnose them early on and avoid jeopardizing the overall success of treatment (Schlitt et al. 2014).

10.1 Introduction

The three preceding chapters, which comprise Part IV of this book, discussed topics falling within the domain of proarrhythmic cardiac safety. As we move into Part V, attention now broadens to other domains within the field of cardiovascular safety. This chapter addresses cardiotoxicity considerations in the therapeutic use of oncologic agents. The construct and employment of benefit–risk assessments have been discussed in several contexts in previous chapters. As we move into discussions related to the therapeutic use of drugs that have received marketing approval, the observation by Garattini (2010) that "drug authorization, prescription, and utilization are all based on benefit-risk assessment" provides an integrated perspective on this topic.

Oncology pharmacotherapy provides a good example of how a drug's benefit–risk balance can be favorable even though the drug has well-acknowledged and relatively severe safety liabilities. Consider a scenario in which a patient has been told that his or her cancer will be terminal in several months, with 6 months being the physician's best guess. Some patients may be willing to take a drug with a sizeable toxicity liability in an attempt to prolong their life by several additional months and/or to improve their quality of life for their remaining time. In this scenario, the risk of cardiotoxicity several years in the future (or even in the short term) may not outweigh the patients' desire to try to maximize their life expectancy and quality of life by obtaining the therapeutic benefit of the drug: they may therefore deem the treatment option to have a favorable benefit–risk balance (Turner and Durham 2009).

However, a different scenario is now much more representative of current oncology pharmacotherapy. Advances on many fronts mean that drugs (sometimes in combination with surgery and/or radiation therapy) are now prolonging patients' lives to a much greater degree. This is a laudable achievement. However, in the context of this chapter's discussions, there is a significant corollary: patients can experience the clinical manifestations of cardiotoxicity on various timelines, including over a decade after cessation of therapy. These manifestations include cardiac dysrhythmias, cardiomyopathy, congestive heart failure, hypertension, ischemia

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and myocardial infarction, pericarditis or myocarditis, and valvular heart disease (Ferri et al. 2013). Cancer survivors therefore represent a population for whom ongoing medical monitoring and surveillance, and prevention or treatment of these clinical conditions, is of marked importance. As Cardinale and colleagues (2013) observed, "Cardiotoxicity due to cancer treatment is of rising concern, for both cardiologists and oncologists, because it may have a significant impact on cancer patient management and outcome."

Two important papers published 25 years ago discussed cardiotoxicity manifesting itself following cessation of treatment with anthracyclines. Lipshultz and colleagues (1991) assessed the cardiac status of 115 children who had previously been treated with doxorubicin for acute lymphoblastic leukemia. Their disease was in continuous remission, and the median interval between cessation of treatment and cardiac evaluation was 6.4 years. Fifty-seven percent of the patients had left ventricular contractility abnormalities, with the cumulative dose of doxorubicin administered during treatment being the most significant predictor of abnormal cardiac function. Eleven patients had congestive heart failure within 1 year of treatment, five had recurrent heart failure between 3 and 10 years after completing treatment, and two required heart transplantation. The authors concluded as follows: "Doxorubicin therapy in childhood impairs myocardial growth in a dose-related fashion and results in a progressive increase in left ventricular afterload sometimes accompanied by reduced contractility. We hypothesize that the loss of myocytes during doxorubicin therapy in childhood might result in inadequate left ventricular mass and clinically important heart disease in later years" (Lipshultz et al. 1991).

Steinherz and colleagues (1991) examined cardiac toxicity in 201 long-term survivors of pediatric malignancies between 4 and 20 years after completing anthracycline therapy: the median time from completion of treatment was 7 years. Echocardiography revealed that 23 % of the patients had abnormal cardiac function, and cumulative dose was again associated with the incidence of abnormalities. Of the original 201 patients, 56 individuals were followed for 10 years or more (with a median of 12 years): 38 %, an even higher percentage, had abnormal findings. The authors concluded that "The 23 % incidence of late cardiac abnormalities warrants continued evaluation of patients after anthracyclines to guide patient care and the design of future chemotherapeutic protocols" (Steinherz et al. 1991). This led to the current box warning for doxorubicin, which reads as follows: "Myocardial damage may lead to congestive heart failure and may occur as the total cumulative dose of doxorubicin HCl approaches 550 mg/m^2. The risk of cardiomyopathy may be increased at lower cumulative doses with mediastinal irradiation" (Doxorubicin Package Insert 2016).

Across the next two decades, evidence continued to accumulate that "Cardiac disease in patients with cancer is common and influences the longevity and quality of life both of patients in active treatment and of survivors of cancer," and, within the therapeutic specializations of cardiology and oncology, there was increasing recognition of the benefits to patients of cardiologists and oncologists collaborating in the care of cancer patients with cardiac disease (Lenihan et al. 2010). This recognition led to the creation of the International CardiOncology Society, which was founded at a conference in Milan, Italy, in 2009 (Lenihan et al. 2010).

10.2 Cardiac Imaging Techniques

Heart abnormalities, whether drug-induced or not, require methods of assessment. Christian and colleagues (2012) discussed three commonly used imaging modalities: echocardiography, magnetic resonance imaging (MRI), and radionuclide (nuclear) imaging. Each is discussed in turn.

10.2.1 Echocardiography

Echocardiography is a widely applied noninvasive modality that provides data on cardiac structure and function. Two-dimensional (2D) echocardiography with Doppler flow assessments can characterize hemodynamics and systolic/diastolic function and display cardiac structures and measurements of cardiac chamber sizes. Three-dimensional (3D) echocardiography offers the potential to enhance assessments of cardiac function, structure, and geometry.

The echocardiography measurement modality has both advantages and disadvantages. Advantages include the following:

- It is easily performed, widely available, relatively inexpensive, and highly portable. There is no ionizing radiation, and there are no limitations with regards to patients' experiencing claustrophobia or with existing metallic implants.
- While the use of contrast agents enhances image quality and reduces variability, they are generally not required except when image quality is particularly poor.
- It provides real-time data and is a preferred method when frequent assessments are required.
- It provides detailed information on cardiac structure (atrial and ventricular cavity dimensions, areas, volumes, wall thickness, and mass), cardiac function (systolic and diastolic, right and left ventricular wall motion, fractional shortening and ejection fraction, global and regional, and preload and afterload), valvular disease (structure, function, and degree of regurgitation or stenosis), vascular structures, and hemodynamic data.

Disadvantages include the following:

- Image variability. Sources of variability during image acquisition include the skill level of the sonographer, employment of different machines or imaging modes (e.g., fundamental imaging or harmonic imaging, 2D, or 3D), and biological variability of the patient (e.g., changes in preload or afterload). During image interpretation, sources include the algorithms used (e.g., single-plane or biplane method for left ventricular ejection fraction) and inter-reader variability. During chemotherapy in patients with advanced cancer, marked changes in intravascular volume status, heart rate, or blood pressure also potentially contribute to increased variability in serial assessments.

- Image quality. Poor acoustic windows can result in poor visualization of the left ventricular endocardial border, making quantitation of LVEF difficult or inaccurate: this can happen in up to 10 % of patients (Christian et al. 2012).

10.2.2 Magnetic Resonance Imaging

Cardiac magnetic resonance imaging (MRI) is an accurate, reproducible, and well-validated technique for measuring left and right ventricular volumes and mass and is a recognized imaging modality for many cardiovascular applications (Pennell et al. 2004). Advantages include the following: production of high-resolution images, precision that is reliable even after cardiac remodeling, high reproducibility, and comprehensive data collection. With regard to the last advantage listed, cardiac MRI provides comprehensive structural and functional data including left and right ventricular dimensions, volume, mass, and systolic function, and degree of myocardial fibrosis and/or inflammation. Disadvantages include its higher cost relative to echocardiography and nuclear imaging, potentially limited access, and contraindications. Contraindications include patients' claustrophobia, metallic implants (e.g., pacemakers, defibrillators, insulin pumps, aneurysm clips, and any other foreign metallic objects), and limitation in large body size (Christian et al. 2012).

10.2.3 Radionuclide (Nuclear) Imaging

Nuclear imaging has a long history of employment in detection and monitoring of chemotherapy-induced cardiotoxicity (Alexander et al. 1979). Advantages of this modality include that it is relatively operator independent, less expensive than MRI, and a well-established standard for monitoring left ventricular function. Accuracy and precision of left ventricular systolic function is good, and hence reproducibility of LVEF measurements is good. Disadvantages include the following:

- It is expensive compared with echocardiography.
- It is not as readily available as echocardiography. Treatment centers' availability of and expertise in specific nuclear imaging modalities vary.
- It requires exposure to ionizing radiation, which can be especially limiting when multiple occasions of measurement are needed.
- It provides limited information on cardiac anatomical details.

10.3 Biomarkers

Lenihan and Cardinale (2012) grouped the multiple potential cardiovascular complications of oncologic therapy into three main categories:

- Vascular conditions: these include atherosclerosis, thrombosis, and hypertension and are predominant.
- Cardiac structural problems: these, especially valvular degeneration, can have a dramatic long-term impact.
- Cardiac dysfunction and heart failure: these potentially common late effects can be prevented or detected early during active cancer therapy to result in optimal patient outcomes.

The authors emphasized the importance of the latter category precisely because of the benefits of early identification and appropriate intervention. They also observed that future research on late cardiac effects in cancer survivors needed to include "advanced cardiac imaging techniques, novel cardiac biomarkers, and genetic determinants of response to cancer treatment" (Lenihan and Cardinale 2012). This section discusses biomarkers.

Decisions to investigate the potential utility of existing biomarkers and their associated assays have typically been predicated on their employment in assessing cardiac dysfunction in other settings, such as ischemia and heart failure (Morrow et al. 2007; Yancy et al. 2013). Biomarkers of interest in this domain include troponin (cTn), natriuretic peptides, glycogen phosphorylase BB (GPBB), myeloperoxidase (MPO), and circulating microRNAs (Christenson et al. 2015).

While echocardiography is currently commonly used to assess cardiac function prior to and during therapy with anthracyclines, this technique is acknowledged to be insensitive. Normal hearts "have excellent reserve capacity, so even modest loss of left ventricular function is indicative of significant cardiovascular damage" (Christenson et al. 2015; see also Ewer and Lenihan 2008). Moreover, as more individuals receive chemotherapy, it is not currently possible to differentiate to a desirable degree the progression of underlying cardiac disease from drug-induced cardiotoxicity. Therefore, much attention is currently focusing on biomarkers that may have predictive value in the early detection of cardiotoxicity. Christenson and colleagues (2015) commented that, at present, "there is no effective means of accurately detecting and predicting myocardial damage occurring with chemotherapy." Biomarkers have the potential to fill this void, allowing for risk stratification of patients to distinguish those at increased susceptibility for side effects of therapy, in whom lower doses are warranted, from patients for whom more aggressive chemotherapeutic regimens can be entertained (Christenson and colleagues, 2015).

10.3.1 Cardiac Troponin

Circulating cardiac troponin (cTn) is the most widely used biomarker for detection of myocardial injury (Newby et al. 2011). With regard to its employment in the context of drug-induced cardiotoxicity, most data to date have examined anthracycline-based chemotherapy, and so the broader applicability of these data is currently uncertain (Christenson et al. 2015). However, a notable 2004 publication from the Expert Working Group on Biomarkers of Drug-induced Cardiac Toxicity (Wallace et al. 2004) reported that troponin I (cTnI) and troponin T (cTnT) are sensitive, specific, and robust biomarkers of drug-induced cardiotoxicity.

Blaes and colleagues (2015) reported a study examining the utility of various biomarkers, including high-sensitivity cTnT, in patients receiving anthracycline therapy to investigate whether baseline levels or changes were informative in the prediction of the onset of congestive heart failure. Elevations in baseline high-sensitivity cTnT were suggestive of a subgroup of oncology patients at high risk of developing drug-induced cardiotoxicity. Noting that the optimal treatment for drug-induced cardiotoxicity is prevention, the authors observed that "early detection with the use of biomarkers remains crucial in evaluating these patients, and in potentially introducing interventions to prevent these long-term complications" (Blaes et al. 2015).

10.4 Examples of the Cardiotoxicity of Oncologic Drugs

Table 10.1 provides some examples of cardiotoxicity information listed in drug labels of oncologic drugs and biologics. These examples include QT prolongation/*torsades*, hypertension, and cardiomyopathy, each of which is then discussed in more detail.

*10.4.1 QT Interval Prolongation/*Torsades

QT interval prolongation and *torsades* are listed for several of the examples presented in Table 10.1. Of particular relevance here are earlier discussions in Sect. 7.6.1 addressing approaches taken when the standard TQT was not feasible, including cases where the test drug cannot ethically be given to healthy participants, the population that participates in TQT studies. Such a modified approach has been the case for oncologic drugs during the proarrhythmic cardiac safety regulatory landscape circa 2005–2015 discussed in Chap. 7. Going forward, if, as seems likely, the exposure–response methodology discussed in Chap. 8 assumes prominence in the preapproval clinical assessment of QT interval prolongation, one assumes the same caveat will apply. In cases where the potential therapeutic benefit of a drug intended to address a serious and unmet medical need is considered by regulators to outweigh the known cardiac risk (and the drug has an acceptable general safety profile), it will

Table 10.1 Examples of cardiotoxicity information in drug labels

Drug (class)	Parameters mentioned in the "highlights of prescribing information"
Bevacizumab (vascular endothelial growth factor-specific angiogenesis inhibitor)	Arterial thromboembolic events, e.g., myocardial infarction, cerebral infarction, hypertension
Doxorubicin (anthracycline topoisomerase inhibitor)	Acute left ventricular failure, heart failure, cardiomyopathy (note: information presented in Sect. 5.1 of the full prescribing information) *Boxed warning: cardiomyopathy*
Lapatinib (kinase inhibitor)	QT prolongation possible in some patients, decreased left ventricular ejection fraction
Nilotinib (kinase inhibitor)	QT prolongation, sudden deaths in patients with resistant or intolerant Ph + CML (ventricular repolarization abnormalities may have contributed to their occurrence) *Boxed warning for QT prolongation and sudden deaths*
Pazopanib (kinase inhibitor)	QT prolongation and TdP, congestive heart failure and decreased left ventricular ejection fraction, hypertension, fatal hemorrhagic events, arterial thrombotic events
Sorafenib (kinase inhibitor)	Hypertension, cardiac ischemia, and/or infarction may occur
Sunitinib (kinase inhibitor)	QT prolongation and *torsades*, cardiac toxicity including left ventricular ejection fraction declines to below the lower limit of normal and cardiac failure including death, hypertension, hemorrhagic events
Vandetanib (kinase inhibitor)	QT prolongation, *torsades*, and sudden death, heart failure, hemorrhage, hypertension *Boxed warning for QT prolongation, torsades, and sudden death* REMS in place

Modified from Turner et al. (2014)

receive regulatory approval for marketing, albeit with the addition of a precautionary statement in the package insert, a black box warning, and/or requirements associated with a risk evaluation mitigation strategy (REMS) designed to make therapeutic employment of the drug as safe as is possible (the topic of REMS is addressed in Chap. 12). As an example presented in Table 10.1, this information is in the label for vandetanib, a kinase inhibitor indicated for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable, locally advanced or metastatic disease.

10.4.2 Hypertension

Epidemiological studies have suggested that an increase of 3 mmHg in blood pressure is associated with a 10–20 % increase in congestive heart failure (ALLHAT Collaborative Research Group 2000). Conversely, a 3–4 mmHg reduction in blood pressure in hypertensive individuals decreases risk of myocardial infarction by 22 % and of stroke by 33 % (Heart Outcomes Prevention Evaluation Study Investigators

2000). Currently, there is no consensus concerning the clinical significance of an off-target drug-induced increase in blood pressure of these magnitudes in healthy patients in whom the pressure remains within the normotensive range. Nonetheless, it is possible that small drug-induced blood pressure increases may have significant impact in patients with enhanced cardiovascular risk due to older age, cardiovascular comorbidities, or other traditional cardiovascular risk factors. Consequently, off-target drug-induced blood pressure elevations induced by multiple drug classes have increasingly attracted scientific interest (Grossman and Messerli 2012; O'Brien and Turner 2013; Sager et al. 2013), and this topic is therefore discussed in further detail in the following chapter. Here, attention focuses on blood pressure increases induced by oncologic agents.

Hypertension is the most common adverse effect of antivascular endothelial growth factor (anti-VEGF) agents that either bind to circulating VEGF or inhibit tyrosine kinases associated with VEGF receptors stimulated by VEGF proteins. This group includes VEGF binding agents such as the monoclonal antibody bevacizumab, the recombinant fusion protein aflibercept, and the multi-targeted kinase inhibitors (MTKIs), e.g., axitinib, pazopanib, sorafenib, sunitinib, and vandetanib. These VEGF-targeted therapies cause hypertension in 30–80 % of patients. Unlike traditional "off-target" side effects, hypertension is a mechanism-dependent, "on-target" toxicity, reflecting effective inhibition of the VEGF signaling pathway rather than nonspecific effects on unrelated signaling pathways (Robinson et al. 2010). The exact factors that predispose to VEGF inhibitor (VEGFI)-induced hypertension still remain to be established. However, risk factors that have been associated with VEGFI-induced hypertension include a previous history of hypertension, combination therapy with more than one anti-VEGFI, aged 65 years or older, smoking, and possibly high cholesterol (Small et al. 2014). The actual cause of elevated blood pressure is multifactorial, with decreased nitric oxide production, reduction in the density of microvascular beds, loss of antioxidative effect, reduced prostacyclin production, capillary rarefaction, and activation of the endothelin-1 system being suggested as possible mechanisms.

Hurwitz and colleagues (2004) investigated the safety of bevacizumab plus irinotecan, fluorouracil, and leucovorin for the treatment of metastatic colorectal cancer, reporting that severe hypertension (blood pressure >200/100 mmHg) was three to five times higher as compared with the placebo group. In an observational cohort study, the Bevacizumab Regimens' Investigation of Treatment Effects (BRiTE) study, de novo hypertension was observed in 22 % of patients: 18.7 % of patients with pre-existing hypertension experienced worsening of the condition (Kozloff et al. 2009). Sorafenib, approved for advanced renal cell carcinoma and hepatocellular carcinoma, has been reported to increase mean systolic blood pressure by 8.2 mmHg and diastolic blood pressure by 6.5 mmHg within 24 h of treatment with 400 mg given twice a day: hypertension occurred in 23.4 % of patients on sorafenib, with severe hypertension seen in 5.7 % (Wu et al. 2008). Respective figures of 21.6 and 6.8 % have been reported for sunitinib (Zhu et al. 2009). Sunitinib is indicated for several conditions: gastrointestinal stromal tumor after disease progression or intolerance to imatinib mesylate, advanced renal cell carcinoma, and progressive,

well-differentiated pancreatic neuroendocrine tumors in patients with unresectable locally advanced or metastatic disease.

10.4.3 Cardiomyopathy and Left Ventricular Dysfunction

Cardiomyopathies include a heterogeneous group of myocardial diseases associated with mechanical and/or electrical dysfunction. They usually exhibit inappropriate ventricular hypertrophy or dilatation and can be further classified into dilated, hypertrophic, restrictive, and arrhythmogenic right ventricular cardiomyopathy according to morphological and functional criteria (Thiene et al. 2008).

While several oncologic drugs have been associated with cardiomyopathy, anthracyclines such as daunorubicin and doxorubicin are salient examples. Anthracycline-induced cardiotoxicity may be defined as acute, early-onset chronic, and late-onset chronic (Cardinale et al. 2015). Acute cardiotoxicity occurs after a single dose, or a single course, of anthracyclines, and the onset of clinical manifestations is within 2 weeks from the end of treatment. Early-onset chronic toxicity develops within 1 year, and is the most frequent and clinically relevant form of cardiotoxicity. It usually presents as a dilated and hypokinetic cardiomyopathy leading to heart failure. Late-onset chronic cardiotoxicity develops years, or even decades, after the end of chemotherapy (Cardinale et al. 2015).

Acute cardiotoxicity is seen in approximately 1 % of cancer patients. The cardiotoxicity manifests as acute pericarditis/myocarditis. Characteristics include a transient decline in indices of myocardial contractility as seen by the employment of echocardiography and the combination of alterations in the ST segment and T-wave morphology in conjunction with prolongation of the QT interval as seen on the ECG. Early-onset chronic cardiotoxicity, which is dose dependent, has been reported in 1.6–2.1 % of patients: late-onset cardiomyopathy is observed in up to 5 % of patients (Curigliano et al. 2012).

Cardiotoxicity of oncologic drugs can be classified as irreversible (type I) or reversible (type II) dysfunction (Suter and Ewer 2013). Type I cardiotoxicity occurs due to cell loss which induces the progressive myocardial dysfunction classically seen with anthracyclines (Yusuf et al. 2011). Type II cardiotoxicity results from cellular dysfunction that is usually reversible and associated with normalization of cardiovascular function on completion of therapy. Anti-human epidermal growth factor receptor 2 (HER2) agents (e.g., pertuzumab, lapatinib, ado-trastuzumab) typically cause type II cardiotoxicity. Trastuzumab usually produces type II toxicity but may cause type I toxicity in patients with pre-existing heart disease or prior anthracycline therapy (Curigliano et al. 2012). Trastuzumab use typically results in small to modest risk for cardiotoxicity, which is typically manifested by an asymptomatic decrease in left ventricular ejection fraction and less often by clinical heart failure. Although limited, available data for pertuzumab and ado-trastuzumab support the view that they may be less cardiotoxic than trastuzumab.

Establishing the diagnosis of cardiomyopathy in patients undergoing active cancer treatment is often challenging, as common symptoms and signs such as fatigue, dyspnea, increased jugular venous distension, and lung crepitations may be due to other causes (Ferri et al. 2013). Useful noninvasive diagnostic modalities for diagnosing chemotherapy-induced cardiomyopathy include echocardiography, radionuclide ventriculography, multiple-gated acquisition computed tomography scans, and magnetic resonance imaging scans (Raschi et al. 2010; Yusuf et al. 2011). Since some drug-induced cardiomyopathy is irreversible, the employment of biomarkers may help identify myocardial damage prior to a decline in left ventricular ejection fraction (Gottdiener et al. 2004). Increased serum levels of cardiac troponin can help identify patients who may subsequently develop a reduction in LVEF (Florea and Anand 2012).

10.5 Therapeutic Management

Mounting evidence suggests that trastuzumab, especially when given in combination with anthracyclines, has been associated with both asymptomatic and symptomatic left ventricular dysfunctions that can lead to premature discontinuation of trastuzumab therapy and significant cardiac morbidity. Seicean and colleagues (2013) retrospectively evaluated the incidence of new symptomatic heart failure in patients with breast cancer treated with anthracyclines, trastuzumab, or both, at an academic medical center between 2005 and 2010. Using 1:2 propensity matching, patients on continuous β-blockers during cancer treatment were compared with those not on β-blockade. The effect of incidental β-blocker use on new symptomatic heart failure and noncardiac mortality was assessed during a median follow-up of approximately 3 years. Results showed that trastuzumab, when given alone or in combination with anthracyclines, substantially increased the risk of symptomatic heart failure compared with anthracyclines alone. Furthermore, incidental β-blocker use significantly reduced the incidence of symptomatic heart failure, but did not affect noncardiac mortality in patients with breast cancer treated with trastuzumab, anthracyclines, or both.

10.5.1 Strategies for the Prevention of Anthracycline- and Trastuzumab-Induced Cardiotoxicity

Current strategies to prevent cardiac toxicity include limiting the cumulative anthracycline dose, prolonging infusion times to limit peak serum concentrations of anthracyclines, using liposomal formulations of anthracyclines, administering anthracyclines and trastuzumab sequentially rather than concurrently, and using non-anthracycline-based chemotherapy regimens for the treatment of HER2+ breast cancer. However, despite these attempts, cardiotoxicity remains prevalent. The iron

chelator dexrazoxane is the only drug currently approved to prevent anthracycline-induced cardiomyopathy. However, its use in clinical practice is limited by concerns of myelosuppression and reduced tumor response rates. Beta-adrenergic antagonists have also been added to this list of promising agents (Seicean et al. 2013).

Further evidence for the emerging role of prophylactic β-blocker therapy for mitigating the effect of trastuzumab on left ventricular function comes from the recently reported results of the Multidisciplinary Approach to Novel Therapies in Cardiology Oncology Research (MANTICORE) trial (Pituskin 2015). This Phase III trial was designed to determine whether prophylactic use of a β-blocker or an ACE inhibitor (two drugs used to treat established cardiovascular disease) could reduce trastuzumab-associated cardiotoxicity in patients with HER2-positive early breast cancer. At baseline, all patients had a left ventricular ejection fraction ≥ 50 %. Patients were randomized to receive bisoprolol, perindopril, or placebo during trastuzumab-based chemotherapy for 24 months. Cardiac magnetic resonance imaging parameters (see Sect. 10.4.2) were assessed at baseline, at 3 months, at 12 months, and at 24 months. Mean age at baseline was approximately 50 years. Bisoprolol significantly prevented reduction from baseline in left ventricular ejection fraction vs. placebo and also prevented trastuzumab interruptions due to a drop in left ventricular ejection fraction. However, since it did not prevent left ventricular remodeling (as measured by left ventricular end diastolic volume) associated with trastuzumab therapy, more research is needed on optimal cardioprotection for patients receiving trastuzumab.

10.5.2 Therapeutic Management of Hypertension

As more cancer patients are treated with VEGFIs, and more potent VEGFIs are developed, the burden of hypertension toxicity will increase. This will be further compounded as the use of antiangiogenic drugs broadens to include older patients and those with cardiovascular risk factors and pre-existing hypertension (Small et al. 2014). While there are currently no widely accepted guidelines addressing VEGFI-induced hypertension, several authors have addressed this issue.

Steingart and colleagues (2012) reported recommendations for physicians from the Cardiovascular Toxicities Panel of the National Cancer Institute (NCI). These included the following:

- Conduct and document a formal risk assessment for existing cardiovascular disease and potential cardiovascular complications before starting VEGFI treatment, recognizing that pre-existing hypertension and cardiovascular disease are common in patients with cancer.
- Actively monitor for blood pressure elevations and cardiac toxicity with more frequent assessments during the first VEGFI treatment cycle.
- Aggressively manage blood pressure elevations and early symptoms and signs of cardiac toxicity to prevent clinically limiting complications of VEGFI therapy.

Small and colleagues (2014) noted that in the absence of specific guidelines, angiotensin-converting enzyme inhibitors and dihydropyridine calcium channel blockers (e.g., amlodipine, nifedipine) are commonly used as antihypertensive agents in this setting. Their review concluded that "expert opinion recommends that patients be fully assessed for hypertension and cardiovascular disease before VEGFI treatment, that blood pressure is monitored frequently, and that hypertension is aggressively treated to target (<140/90 mmHg)" (Small et al. 2014).

Rutkowski and Stepniak (2016) focused on regorafenib, a multi-targeted inhibitor with activity against multiple kinases that has demonstrated clinical benefit in gastrointestinal stromal tumor (GIST) patients after progression on prior treatment with at least imatinib/sunitinib, currently the approved standard third-line option in therapy of advanced GIST. They provided expert opinion on the management of several adverse events, including liver toxicity and hypertension. Management strategies for hypertension included dose reduction and the use of antihypertensive agents and, if necessary, cessation of therapy. They also noted that "Patients should be counseled on the risks of serious adverse events associated with regorafenib and advice should be given to health care providers on patient monitoring" (Rutkowski and Stępniak 2016).

10.6 Early Detection of Cardiotoxicity: Heart Failure

Lenihan and Cardinale (2012) grouped the multiple potential cardiovascular complications of oncologic therapy into three main categories:

- Vascular conditions: these include atherosclerosis, thrombosis, and hypertension and are predominant.
- Cardiac structural problems: these, especially valvular degeneration, can have a dramatic long-term impact.
- Cardiac dysfunction and heart failure: these potentially common late effects can be prevented or detected early during active cancer therapy to result in optimal patient care.

As noted previously, cardiac dysfunction and heart failure are potentially common late effects of oncologic therapy (Lenihan and Cardinale 2012). The authors emphasized the importance of the latter category precisely because of the benefits of early identification and appropriate intervention. Cardinale and colleagues (2015) conducted a prospective study addressing the early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. In the study, including 2,625 participants initially, individuals were followed up after the last dose of anthracycline-containing therapy: the median follow-up period was 5.2 years (range: 4 months to 19 years). Two hundred and twenty-five (9 %) participants were lost to follow-up. Of the rest, cardiotoxicity occurred in 226 (9 %). The median time between cessation of treatment and the development of cardiotoxicity was 3.5 months.

Heart failure therapy was initiated in all individuals who developed cardiotoxicity. Treatments included enalapril, enalapril plus carvedilol, and enalapril plus biso-

prolol. Oral diuretics were added to therapy in 20 % of the cases. Eighty-two percent of the patients recovered from cardiotoxicity (mean time to recovery: 8 ± 5 months). Of those, 11 % had full recovery and 71 % had partial recovery. Those who did not recover had a higher New York Heart Association classification of disease, and they had a higher incidence of adverse cardiac events. The authors commented as follows (Cardinale et al. 2015):

> The most important results of the present study were that anthracycline-induced cardiotoxicity occurred in 9% of adult treated patients, it was dose dependent, and its highest incidence was observed during the first year after the completion of chemotherapy. Another important finding was that close monitoring of cardiac function during this period allowed early detection and treatment of cardiotoxicity, with major LVEF improvement in most cases.

10.7 The Discipline of Cardio-oncology

Lenihan et al. (2010) published a paper describing the creation of the International CardiOncology Society to facilitate an effective partnership between the medical disciplines of cardiology and oncology. (The term cardio-oncology is often seen in the literature now and is adopted in this chapter.) The society's creation was in line with the increasing recognition of the benefits of doctors from these disciplines in the care of cancer patients with cardiac disease (Lenihan et al. 2010). This new field has continued to grow. Curigliano and colleagues (2016) observed as follows:

> The discipline of cardio-oncology has developed in response to the combined decision making necessary to optimize the care of cancer patients, whether they are receiving active treatment or are long-term survivors. Strategies to prevent or mitigate cardiovascular damage from cancer treatment are needed to provide the best cancer care. This review will focus on the common cardiovascular issues that may arise during or after cancer therapy, the detection and monitoring of cardiovascular injury, and the best management principles to protect against or minimize cardiotoxicity during the spectrum of cancer treatment strategies.

This quote also highlights the term long-term survivors, individuals who are cancer-free for long periods of time following cessation of treatment but who are unfortunately not immune to late-occurring treatment toxicities. Rowland and colleagues (2013) used the term survivorship science to refer to several aspects of work in this field, including the infrastructure needed to sustain and advance such work, platforms for research, assessment tools, and vehicles for the dissemination of findings.

10.7.1 Prevention or Mitigation of Cardiovascular Damage and Its Relationship to Oncologic Agents' Efficacy

In cases where there is a medical need to use an oncologic agent that can cause cardiotoxicity, one strategy is the coadministration of a drug that will not decrease the efficacy of the oncologic agent to an unacceptable degree and will also prevent

or mitigate potential cardiovascular damage. A recently reported double-blind, randomized trial evaluated the preventive effects of carvedilol on doxorubicin-induced cardiotoxicity (Tashakori Beheshti et al. 2016). A total of 70 female patients with breast cancer participated, with 30 receiving chemotherapy plus carvedilol and 40 receiving chemotherapy plus placebo. Both treatment groups were evaluated 1 week before and 1 week after chemotherapy utilizing measurement of left ventricular ejection fraction via assessments of strain and strain rate. Strain echocardiography is a new technology that facilitates improved accuracy in the calculation of left ventricular ejection fraction (see Curigliano et al. 2016). After chemotherapy there was no statistically significant difference in strain and strain-rate measures in the carvedilol treatment group. In contrast, there were statistically significant decreases in the placebo treatment group. The authors concluded that the results showed that carvedilol can prevent doxorubicin-induced cardiotoxicity while also noting "Whether this prophylaxis should be considered as the preferred method needs further investigation" (Tashakori Beheshti et al. 2016).

Nonclinical research is also of interest in this domain. Arsenic trioxide (ATO) is efficacious in the treatment of patients with acute promyelocytic leukemia but is associated with cardiotoxicity. It has previously been documented that morphine has antioxidant, antiapoptotic, and cytoprotective properties and is able to attenuate cytotoxicity. Therefore, Amini-Khoei and colleagues (2016) employed cardiomyocytes to investigate the potential attenuation of ATO-induced cardiotoxicity by morphine. The authors reported that morphine attenuated ATO-induced cytotoxicity and suggested that morphine may have protective properties when the drug is used in humans as an oncologic agent.

A key question when using a second agent to prevent or mitigate cardiotoxicity is whether the second agent decreases the efficiency of the oncologic agent. Smith and colleagues (2016) noted that several drugs are currently in use clinically in this regard, including angiotensin-converting enzyme inhibitors, beta-blockers, metformin, and dexrazoxane. Breast cancer cell lines were treated with a range of concentrations of doxorubicin alone or doxorubicin plus trastuzumab in the presence of clinically relevant doses of enalapril, carvedilol, metformin, or dexrazoxane, and cell survival was determined. On the basis of their data the authors concluded that the cardioprotective drugs tested do not interfere with the anticancer efficacy of doxorubicin or trastuzumab but also noted that "further studies to establish the effect of cardioprotective drugs on anticancer drug efficacy would be beneficial" (Smith et al. 2016).

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Chapter 11

Blood Pressure Responses to Noncardiovascular Drugs in Development and Therapeutic Use

A variety of therapeutic agents or chemical substances may increase blood pressure… When use of a chemical agent which increases blood pressure is mandatory, anti-hypertensive therapy may facilitate continued use of this agent (Grossman et al. 2015).

11.1 Introduction

This chapter focuses on unintended drug-induced blood pressure responses. While both increases and decreases are legitimate areas of investigation (Kane-Gill et al. 2014; Kennelly and Esaian 2013), our attention falls on increases. As was noted in Sect. 3.4.4, high blood pressure is authoritatively regarded as the greatest threat to the global burden of disease (Horton 2013; Das and Samarasekera 2013; Lim et al. 2013). As hypertension has been studied across several decades, we have learned that there are multiple ways in which increased blood pressure may occur (see Frohlich 1977; Page 1982; Dustan 1990; Harrison 2013). It has now also become clear that noncardiovascular drugs can lead to off-target increases in blood pressure and can also do so via a variety of mechanisms of action. As Grossman and Messerli (2012) observed, "Some agents cause either sodium retention or extracellular volume expansion, or activate directly or indirectly the sympathetic nervous system. Other substances act directly on arteriolar smooth muscle or do not have a defined mechanism of action. Some medications that usually lower BP may paradoxically increase BP, or an increase in pressure may be encountered after their discontinuation."

Two issues are addressed in this chapter. First, as we write this chapter, there is not a regulatory landscape in place addressing the prospective exclusion of unacceptable blood pressure increases. However, what might sensibly be done during drug development to identify signals of drug-induced blood pressure increases is addressed. Second, when such increases are identified, what strategies might be employed by physicians in clinical practice? Currently there are no authoritative guidelines, and so we provide expert opinion from Professor Michael Weber.

J.R. Turner et al., *Cardiovascular Safety in Drug Development and Therapeutic Use*, DOI 10.1007/978-3-319-40347-2_11

11.2 Drug-Induced Blood Pressure Changes

We noted in the previous chapter that some oncologic agents are associated with blood pressure increases, and examples were provided in Table 10.1. Table 11.1 provides additional examples from multiple drug classes.

There are clear reports of clinical concern. Grossman and Messerli (Grossman and Messerli 2012), for example, observed that "severe hypertension involving encephalopathy, stroke, and irreversible renal failure have been reported." However, there is still a lack of systematic study of this area, and the clinical relevance of small, transient drug-induced changes in blood pressure to symptomatology, morbidity, or mortality is not well characterized (O'Brien and Turner 2013).

Interactions between noncardiovascular drugs and antihypertensives are also potential sources of unwanted changes in blood pressure: such interactions may either negate or potentiate the efficacy of an antihypertensive agent. Rifampicin considerably reduces the plasma concentrations and the renin-inhibiting effect of aliskiren and some calcium antagonists by decreasing oral bioavailability. Another example is sitagliptin, a dipeptidyl peptidase IV inhibitor used to reduce hyperglycemia in patients with diabetes, which has been shown to attenuate the blood pressure-lowering effect of high-dose enalapril by stimulating the sympathetic nervous system (Grossman and Messerli 2012).

11.3 Preapproval Investigations of Drug-Induced Blood Pressure Responses

Similarly to the investigation of a noncardiac drug's proarrhythmic liability, investigation of a noncardiovascular drug's liability to increase blood pressure can occur in both nonclinical and clinical development programs. These avenues of research are discussed in turn.

11.3.1 Nonclinical Investigations

While detection of large, obvious changes is not challenging, detecting small and subtle changes is considerably more difficult. Authier and colleagues commented as follows (Authier et al. 2015, p. 222):

> Cardiovascular safety pharmacology has been preoccupied with drug-induced changes in the electrocardiogram, and by comparison there has been little in the way of contemporaneous improvements in the level of complexity and sophistication involved in blood pressure assessment. Thus, it is important to understand the nature of drug-induced changes in blood pressure, appreciate the plethora of agents currently used clinically (and over the counter) that alter blood pressure, and understand safety pharmacology study design in order to optimize assessment of a new chemical entity or biological agent in this context.

Table 11.1 Examples of drugs that affect blood pressure

Drug/drug category	Blood pressure effects
Antidepressants	Several antidepressant agents may increase blood pressure by activating the sympathetic nervous system (SNS). These effects may be more pronounced in older patients and dose dependent
Anti-HIV therapy	Highly active antiretroviral therapy can cause a rise in blood pressure but not usually before 6 months
Drugs activating the SNS	Drugs causing hypertension include phenylephrine hydrochloride (used in upper respiratory decongestants and ophthalmic drops), dipivalyl adrenaline hydrochloride (ophthalmic drops systems), epinephrine (used as bronchodilator, decongestant, in antihemorrhoidal treatment), and phenylpropanolamine (anorexic agent and upper respiratory decongestant)
Drugs for treating addiction	Disulfiram for the management of alcoholism may cause a slight increase in BP, and severe hypertension may occur in patients with alcoholic-induced liver disease
Drugs for treating malignancy	Antivascular endothelial growth factor drugs for the treatment of various malignancies may cause hypertension. About 1 % of all patients on antiangiogenic therapy develop a life-threatening hypertensive crisis
Erythrocyte-stimulating agents	Erythrocyte-stimulating agents such as erythropoietin increase BP in as many as 20 % of patients with anemia or chronic kidney disease
Immunosuppressive agents	The incidence of cyclosporine-associated hypertension after renal, bone marrow, and cardiac transplantation varies between 30 % and 100 %. It is also common in patients with autoimmune disease and in patients with psoriasis treated with cyclosporine. Cyclosporine-induced hypertension is characterized by disturbance of the circadian rhythm, with the absence or reversal of the normal nocturnal fall in blood pressure. Hypertension usually decreases after the withdrawal or substitution of cyclosporine immunosuppression but may not remit completely
Nonsteroidal anti-inflammatory	NSAIDs can induce an increase in blood pressure and interfere with antihypertensive treatment, mitigating or abolishing their effect. NSAIDs interfere with some antihypertensive agents such as diuretics, beta-blockers, and angiotensin-converting enzyme inhibitors but do not interact with calcium antagonists and central-acting drugs. Significant blood pressure elevations have been seen with acetaminophen in patients with coronary artery disease
Recombinant human erythropoietin (r-HuEPO)	r-HuEPO, which is effective in correcting anemia in patients with end-stage renal failure and patients with malignancies, induces hypertension or worsens existing hypertension in 20–30 % of patients
Sex hormones	Around 5 % of women taking estrogen-containing oral contraceptives develop hypertension (this does not occur with progesterone-only anovulant drugs). Any rise in blood pressure is usually small and reversible on cessation of therapy, but severe hypertensive episodes, including malignant hypertension, may occur
Steroids	Hypertension occurs in at least 20 % of patients treated with synthetic corticosteroids in a dose-dependent fashion; oral cortisol at doses of 80–200 mg/d can increase systolic blood pressure as much as 15 mmHg within 24 h
Stimulants	Stimulant drugs for the treatment of attention deficit hyperactivity disorder (amphetamine and dextroamphetamine, atomoxetine, methylphenidate) can raise blood pressure significantly

Modified from tables presented in O'Brien and Turner (2013) and Sager and colleagues (2013)

Nonclinical evaluation of a drug's effects on blood pressure can involve multiple approaches, ranging from in vitro subcellular assays to fully integrated in vivo animal models (Sager et al. 2013). Early exploratory safety pharmacology studies may involve receptor-binding assays (frequently followed by function-based assays) to identify potential off-target effects of drug candidates at sites recognized for modulating vascular tone. Investigations of any potential mechanism(s) to alter kidney sodium handling are also common.

The employment of anesthetized animals facilitates the administration of higher exposures and the use of more extensive instrumentation. It also enables a more thorough hemodynamic evaluation, including assessment of vascular resistance, myocardial contractility, and cardiac output. However, anesthesia itself can have an effect on responses to the drug, generally being associated with greater hemodynamic responses: both conscious and anesthetized animal models can therefore be informative (Authier et al. 2008). Dedicated cardiovascular studies evaluate acute blood pressure effects of drugs in conscious dogs or nonhuman primates: these studies incorporate continuous recording of blood pressure using indwelling catheters.

The use of telemetry systems may prove useful for detecting delayed effects or those resulting from metabolites. The use of trained animals and well-controlled environments can increase the sensitivity and precision of cardiovascular evaluations. The conscious beagle dog model can be useful here due to the peaceful temperament of this animal.

11.3.2 Clinical Investigations of Drug-Induced Blood Pressure Responses

Clinical evaluations of a drug's off-target impact on blood pressure are predicated on several considerations related to the presumed mechanism of action of the blood pressure effects and the intended treatment population (Sager et al. 2013). In this area of investigation, it may not be possible to design a single dedicated study analogous to the employment of a TQT study or a QTc exposure–response study in the domain of proarrhythmic cardiac safety. Identifying potential hemodynamic effects in young healthy participants with heightened sympathetic nervous system activity, for example, may not provide useful information concerning the likely effects seen in older populations, given their lower levels of sympathetic sensitivity (Bhide et al. 2012). The opposite concern is true in the case of nonsteroidal anti-inflammatory drugs: the impact of sodium and volume retention on blood pressure is much less in younger individuals with normal renal handling of sodium and water than in the population most likely to be prescribed chronic therapy, i.e., older individuals with osteoarthritis and pain. Therefore, a "totality of evidence" approach may be the most informative strategy for a comprehensive clinical assessment of off-target blood pressure effects, with attention being paid to both magnitude and duration (Sager et al. 2013).

Several characteristics of Phase I trials have been discussed in previous chapters, and the same advantages and limitations of their nature are seen in this realm of

investigation. With regard to advantages, these studies often see the highest levels of drug exposure. Second, the controlled environment in which they are conducted makes it easier to perform thorough blood pressure assessment: measuring equipment and techniques can be standardized, and measurements timed to blood withdrawals to permit pharmacokinetic information to be collected. Third, collection of repeated blood pressure measurements over time facilitates analysis of change from baseline levels not only at the end of the trial but also at various time points during dosing intervals. Exposure–response relationships can be assessed at both peak and trough drug concentrations.

Limitations of Phase I studies include the small number of participants employed and the consequent limited statistical power and their relatively short duration. Given that the participants are typically relatively young healthy adults (in this setting, the pertinent characteristics of "healthy" are having normal blood pressures and normal renal function), care must be taken when attempting to extrapolate findings to populations most likely to be prescribed treatment, such as older individuals and patients with cardiovascular disease, and to longer durations of exposure to the drug.

Phase II trials still provide the opportunity for rigorous standardization of blood pressure monitoring equipment and technique (something that is more difficult to achieve in Phase III trials). One goal is further investigation of any signal detected in the completed Phase I studies. A second goal results from the employment in Phase II development of individuals with the disease for whom the drug is intended: depending on the mechanism of action of an off-target blood pressure increase, it is therefore possible that a blood pressure signal may be seen in this setting for the first time. Additionally, treatment duration is typically longer than in Phase I studies, the reversibility of any blood pressure effects can be easily determined by programmed assessments after the active treatment period, and since placebo is a commonly used comparator, assessment of the drug's effects on blood pressure can control for regression to the mean and other common confounders (Sager et al. 2013). Phase II is also an opportune time to perform dedicated blood pressure studies that employ out-of-office blood pressure measurement modalities, i.e., home blood pressure monitoring and ambulatory blood pressure monitoring.

Various blood pressure measurement modalities that may be useful in clinical investigations are presented in Table 11.2.

Findings during Phase II development often determine the clinical safety monitoring needs for studies in Phase III development. In this case, they may identify what (if any) additional cardiovascular/hemodynamic evaluations or substudies might be informatively conducted during Phase III development.

Multiple influences in Phase III trials, generated by the use of multiple investigator sites with the likelihood of less rigorous standardization of measurement modalities and techniques, may make it more difficult to evaluate mean blood pressure responses accurately across the larger sample sizes used in these trials. However, they offer a compensatory advantage: the likelihood of the identification of individuals showing particularly large blood pressure increases (outliers) is increased, as is the likelihood of identifying individuals experiencing adverse events that may be due to the drug's effects on their blood pressure. Thus, a richer picture of individual differences can emerge in Phase III trials.

Table 11.2 Blood pressure measurement modalities

Modality	Strengths	Limitations
Clinic blood pressure measurement using auscultation by observer	Traditional standard used in epidemiologic and primary and secondary cardiovascular trials	Poor reproducibility caused by white-coat and masked blood pressure effects. Observer bias. Concern regarding environmental mercury
Clinic blood pressure measurement using noninvasive auscultation devices	Removes environmental concern regarding mercury. Enhanced validation and easier to read the blood pressure column	Poor reproducibility caused by white-coat and masked blood pressure effects. Observer bias
Clinic oscillometric blood pressure measurement (digital)	Removes observer bias. Can select inflation sequence. Improves reproducibility	Precision can be a concern for certain devices, but it is likely improved compared with the first two modalities discussed
Ambulatory blood pressure monitoring	Provides a large number of readings over a 24-h period, thereby enhancing reproducibility. Minimal placebo effect. Obtains blood pressure readings during sleep	Expensive compared with other modalities. Participant adherence related to multiple monitoring sessions can be problematic. Can be a relatively high preponderance of unusable recordings in some studies
Centralized office blood pressure monitoring	Removes some observer bias. Can select inflation sequence. Improves reproducibility. Provides early visibility into blood pressure trends in the clinic	Same as other office-based measurements. Study site education is required to implement process
Self-measured home blood pressure (digital)	Removes white-coat and masked effects. Provides out-of-office readings that can be timed to drug dosing. Correlates to daytime ambulatory blood pressure measurements	Device precision can be a concern with some devices. Requires patient training and requires them to transcribe blood pressure readings into a logbook
Self-measured home blood pressure measurement using telemonitoring	Removes white-coat and masked blood pressure effects. Avoids loss of data by the participants (failure to transcribe readings into the logbook). Ability to transfer and process large amount of data easily. Trend analysis can be performed. Alert criteria can be built into the system	Requires additional training and working with telecommunication providers to move to a data transmission focus

Modified from Sager and colleagues (2013)

Studies employing out-of-office assessments increase the complexity of Phase III development, but they should be incorporated for participant safety and to better characterize the drug's effects if a signal was detected in Phase I and/or Phase II development (Sager et al. 2013).

Assuming that blood pressure data have been ascertained in a consistent manner across the entire Phase III development plan, data pooled across all studies can provide useful additional insights regarding any drug-induced blood pressure changes

over and above those gleaned from individual studies: these include the long-term effects of the drug, mean effects for a participant population, and assessment of individual variation of the effect, most notably a description of the extent of occurrence of outliers. In addition to these blood pressure data themselves, other metrics are informative. For example, discontinuation rates, adverse event reports of hypertension, and the frequency of changes of concomitant antihypertensive medications can be compared between treatment groups. In a large Phase III program, prespecified analyses may yield additional insights regarding important patient subgroups (e.g., the elderly, those with treated hypertension, and African and Hispanic Americans).

11.4 Learning from the Employment of Ambulatory Blood Pressure Monitoring in the Clinical Development of Antihypertensive Agents

The use of ambulatory blood pressure monitoring in pharmacologic trials assessing the efficacy of blood pressure-lowering drugs is now reasonably well established (O'Brien 2011a, 2012). While the intents of trials examining on-target and off-target blood pressure responses differ, i.e., provide compelling evidence of efficacy for antihypertensives and prospectively excluding unacceptable increases in blood pressure for noncardiovascular drugs, the methodological considerations for the employment of ambulatory blood pressure monitoring in the two contexts are very similar, as are the advantages conveyed. We can therefore learn from its use in trials of antihypertensive agents, and the following case study is illuminating.

Since the mechanisms determining blood pressure may differ at different times within the 24-h cycle, it is not surprising that drugs can vary in their effects in these windows of time. The ability of ambulatory blood pressure monitoring to detect blood pressure changes that clinic blood pressure measurement had failed to identify was well illustrated in the Heart Outcomes Prevention Evaluation (HOPE) study (Yusuf et al. 2000; Williams 2000; Svensson et al. 2001). In the main study, the group receiving ramipril had approximately 35 % fewer cardiovascular events, despite an insignificant mean reduction in systolic blood pressure of 3 mmHg and in diastolic blood pressure of 2 mmHg (which can be written as 3/2 mmHg): the outcome benefit was attributed to angiotensin-converting enzyme inhibition, which was recommended in all high-risk individuals regardless of baseline blood pressure. However, it became evident from a later analysis of the ambulatory blood pressure monitoring substudy that ramipril was actually taken in the evening, while clinic blood pressure measurement occurred around 10–14 h later the following morning. The reported insignificant change in blood pressure in the main study gave no indication of a "whopping 17/8 mmHg reduction in BP during the evening hours," which translated into a 10/4 mmHg average reduction over the entire 24-h period (O'Brien 2011b).

O'Brien and Turner (2013) commented on this case study as follows: "The HOPE study was designed to prove the beneficial effect of a drug on cardiovascular outcome, and were it not for the ambulatory blood pressure monitoring study, the

interpretation of the results could have had a major impact on clinical practice." It is not unreasonable to make the case that a similar misinterpretation could occur for blood pressure effects of a noncardiovascular drug if only routine blood pressure measurements during clinical trials were used to assess the drug's effects.

11.5 What Might a Regulatory Landscape Look Like Here?

In an influential Letter to the Editor of the *Drug Information Journal* (now renamed *Therapeutic Innovation & Regulatory Science*), the question of "whether *all* systemically available drugs intended for chronic use merit a careful assessment of their effects on vital signs by [ambulatory blood pressure monitoring]" was raised (Stockbridge 2011). This question has since been discussed in various venues, including a CSRC Think Tank (Sager et al. 2013).

As noted in Sect. 11.1, as we write this chapter there is not a regulatory landscape in place addressing the prospective exclusion of unacceptable blood pressure increases. It is legitimate, however, to speculate what questions a regulatory guidance document would address. Perhaps the following are reasonable possibilities.

Is a pattern of change in both systolic and diastolic blood pressure more important than a (potentially greater) change in either one of them? While it can be reasonably argued that changes induced by drugs taken chronically are of greater concern than those induced by short-term pharmacotherapy, are issues of concern influenced by other variables such as sex and age? Is an increase of X mmHg from a baseline of Y mmHg more, less, or equally concerning than an increase of X mmHg from a baseline of Z mmHg? Is increase of X mmHg from a baseline of Y mmHg or Z mmHg more relevant in the nocturnal period (when risk of cardiovascular events is greatest) than in the daytime period (O'Brien and Turner 2013)?

These questions concern just systolic and diastolic blood pressure levels: we can also add questions concerning pulse pressure (the difference between systolic and diastolic blood pressures), blood pressure variability, and perhaps characteristics such as pulse wave velocity. As already noted, there are many mechanisms that can lead to blood pressure changes, so an additional question arises: is a blood pressure increase caused by mechanism A of more, equal, or less concern than a change of the same magnitude caused by mechanism B, C, or D? The answers to these questions are not readily apparent at this time.

11.5.1 Incorporation of Ambulatory Blood Pressure Monitoring

O'Brien and Turner (2013) offered some thoughts on the inclusion of ambulatory blood pressure monitoring in preapproval clinical development programs, noting that this blood pressure measurement modality provides powerful evidence concerning a drug's blood pressure liability and that it should therefore be a central

component of a "totality of evidence" approach: it facilitates assessments of both magnitude and duration of off-target blood pressure increases.

Employment of ambulatory blood pressure monitoring in clinical trials has financial implications in terms of the cost of the equipment, data evaluation, and staff training and has pragmatic implications in terms of potential inconvenience to participants. However, should a drug receive marketing approval but then be withdrawn for postmarketing safety concerns, the financial ramifications for its sponsor can be considerable, including a considerable decrease in its stock price if it is a publicly traded company. How, then, might a sponsor develop a cost–value–risk mitigation strategy in this context?

Spending some financial resources to conduct ambulatory blood pressure monitoring on at least some clinical trial participants during Phase II seems advisable in both of two possible scenarios. First, the sponsor finds out early that the drug has a blood pressure liability of sufficient magnitude that its benefit–risk balance is unlikely to be favorable, leading to a decision that termination of the drug's development program is judicious. Second, they gain information on the mean magnitude of, and importantly the inter-participant variability in, blood pressure response that allows them to decide most efficiently how many participants should undergo ambulatory blood pressure monitoring in Phase III: the lower the mean magnitude and the lower the inter-participant variability, the smaller the number of participants for whom ambulatory blood pressure monitoring data are likely needed to assuage regulatory concerns and demonstrate a favorable benefit–risk balance should the drug show sufficient efficacy. An integrated portfolio of ambulatory blood pressure monitoring data can then be constructed from Phase II and Phase III investigations and a "totality of evidence" approach taken to their assessment.

11.6 Treatment of Drug-Induced Blood Pressure Increases

In the previous chapter, we discussed how cardiotoxicity due to oncologic agents might be treated by coadministered drugs when the therapeutic benefit of the oncologic agent was medically necessary. The same question is relevant in the context of the present chapter focusing on blood pressure increases due to an array of drugs: how might antihypertensive drugs be used to treat blood pressure increases when the therapeutic benefit of the agent of interest is considered medically necessary?

The literature in this area is not well developed. Writing on behalf of the Italian Society of Hypertension, Virdis and colleagues (2014) observed that "Once drug-induced hypertension is identified, the suspension of the substance or drug is recommended. However, if it is not possible to suspend the administration of these substances, it is often possible to control blood pressure with a titration of antihypertensive therapy". In a similarly general manner, Grossman and colleagues (2015) observed that "Discontinuation of the offending agent will usually achieve adequate blood pressure control. When use of a chemical agent which increases blood pressure is mandatory, anti-hypertensive therapy may facilitate continued use of this

agent." We saw a similar lack of detailed guidance documents in the previous chapter when discussing hypertension induced by oncologic drugs and therefore presented published expert opinions. In this case, we are thankful to Professor Michael A. Weber (Professor of Medicine, State University of New York: Downtown Medical Center, Personal communication, March 16th 2016) for providing the following expert opinion.

There are several reasonable strategies for addressing off-target blood pressure increases. Most simply, if a suitable alternative therapy is available, it should be tried in the hope of avoiding the unwanted blood pressure response. If not, it becomes necessary for the physician and patient to decide together whether the therapeutic benefit of the drug is sufficient to generate a favorable benefit–risk balance and hence justify its continuation. It could be quite reasonable to accept a modest increase in blood pressure for a limited time, perhaps weeks or even a few months, if, in the considered judgment of the physician, the drug's benefits outweigh its risks.

When there is a clear need for longer-term administration of a particular drug, and its off-target blood pressure increase is sufficient to cause clinical concern, the physician must consider possible remedies. Sometimes the patient is already being treated for hypertension, and so dealing with the newly evident rise in blood pressure may be as straightforward as increasing the dosage of the ongoing antihypertensive therapy or possibly adding a further agent to the regimen. Starting new blood pressure-lowering treatment can sometimes be guided by knowing the presumed mechanism of the newfound hypertension. For instance, the elevated blood pressure that can be caused by nonsteroidal anti-inflammatory drugs is at least due partly to renal sodium and water retention: hence, the use of a diuretic may be effective in restoring normal blood pressure. Some classes of drugs can raise blood pressure by stimulating the sympathetic system, again suggesting the use of certain types of antihypertensive agents. However, this could potentially create a new problem if the therapeutic benefits of the agent responsible for increasing the blood pressure depend on its stimulatory effects on sympathetic mechanisms, such that adding the antihypertensive drug might reduce the blood pressure at the price of abolishing the original drug's efficacy. Empirically, one approach to modifying unwanted blood pressure effects is to use a calcium channel blocker such as amlodipine. These agents work largely on the arterial wall and appear to have relatively few systemic effects.

11.6.1 Learning from the Employment of Ambulatory Blood Pressure Monitoring in Routine Clinical Practice

In the present context of identifying and treating drug-induced blood pressure increases, it may be possible to learn from the employment of blood pressure monitoring modalities in routine clinical practice, i.e., for patients whose hypertension is not drug induced.

Consider white-coat hypertension. White-coat hypertension is the phenomenon whereby some individuals not being treated for hypertension show an elevated blood pressure in a physician's office compared with levels in normal daily life (Pickering et al. 1988; Franklin et al. 2013). The term "white coat" reflects that the presence of a physician, or other health-care professional, dressed in the traditional white coat can lead to emotions (e.g., anxiety) that temporarily elevate blood pressure. Such misleading readings can lead to an incorrect diagnosis of hypertension (a false positive). Ambulatory blood pressure monitoring can identify individuals displaying white-coat hypertension in the physician's office and therefore provide cost savings from not treating patients who do not actually need antihypertensive medication because white-coat hypertension was ruled out early on by ambulatory blood pressure monitoring (Krakoff 2006; Lovibond et al. 2011). This rationale formed the basis of the United Kingdom's National Institute for Health and Care Excellence's (NICE's) 2011 guideline for the clinical management of primary hypertension in adults (NICE 2011). In the guideline's section entitled "Diagnosing Hypertension" the following recommendations were made:

- If the clinic blood pressure is 140/90 mmHg or higher, offer ambulatory blood pressure monitoring to confirm the diagnosis of hypertension.
- If a person is unable to tolerate ambulatory blood pressure monitoring, home blood pressure monitoring is a suitable alternative to confirm the diagnosis of hypertension.
- If the person has severe hypertension, consider starting antihypertensive drug treatment immediately, without waiting for the results of ambulatory or home blood pressure monitoring.

Of considerable interest to many health-care professionals in the United States is that the US Preventive Services Task Force (USPSTF) has now released a recommendation statement addressing screening for high blood pressure in adults that includes discussion of ambulatory and home blood pressure monitoring (Siu 2015). The recommendation, which applies to adults 18 years of age and older, makes clear that out-of-office blood pressure measurement is an established and reliable method to confirm an initial diagnosis of hypertension made on the basis of in-office blood pressure measurement. The recommendation is expressed succinctly in the associated clinical summary: "Screen for high blood pressure; obtain measurements outside of the clinical setting for diagnostic confirmation." The recommendation received the USPSTF's grade A rating, indicating their belief that there is high certainty of net benefit from following the recommendation. Ambulatory blood pressure monitoring was considered to be the best confirmatory test for hypertension: the alternative of home blood pressure monitoring may also be a reasonable strategy, although there was considered to be less evidence supporting its value (Siu 2015).

It seems reasonable to assume that the identification of drug-induced blood pressure increases of clinical concern would best be done via employment of ambulatory blood pressure monitoring, which provides a 24-h blood pressure profile.

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Chapter 12

The Genesis of Cardiovascular Safety Regulatory Landscapes for New Antidiabetic Drugs for Type 2 Diabetes

A meta-analysis is always considered less convincing than a large prospective trial designed to assess the outcome of interest (Nissen and Wolski 2007).

12.1 Introduction

The noncommunicable disease of diabetes mellitus has reached epidemic proportions, and it knows no geographic boundaries (Turner 2014). Diabetes, a chronic disorder characterized by elevations in both basal and postprandial (post-meal) glucose levels, is associated with a two- to fourfold increased risk of cardiovascular disease and a threefold increased risk of mortality (Meigs 2003). There are two major forms of diabetes, type 1 and type 2. The typical age of onset of type 1 diabetes is in childhood. This form is also known as insulin-dependent diabetes since patients do not produce enough insulin for healthy function: multiple daily injections of insulin (i.e., exogenous insulin) are required to maintain life, and strict dietary rules, planned physical activity, and daily home glucose tests are also necessary.

The characterization of type 2 diabetes has changed over recent years. Previously used terms such as non-insulin-dependent diabetes and adult-onset diabetes are no longer appropriate: some individuals with type 2 diabetes do require insulin, and children now have this form of the disease. It is characterized by decreased insulin secretion and insulin resistance, a condition in which insulin is not able to carry out its functions effectively, i.e., it cannot decrease plasma glucose levels via suppression of hepatic glucose and stimulation of glucose use in skeletal muscle and adipose tissue.

As one example from a country in the Western world, the US National Diabetes Statistics Report, 2014, observed that in 2012, 29.1 million Americans (9.3 %) had diabetes and that 86 million individuals aged 20 years and older had prediabetes: the respective figures for just 2 years earlier were 25.8 million (8.3 %) and 79 million (CDC 2014). Type 1 diabetes has long been a disease observed in pediatric populations, but, as noted a few moments ago, the same is now true for type 2 diabetes. The

J.R. Turner et al., *Cardiovascular Safety in Drug Development and Therapeutic Use*, DOI 10.1007/978-3-319-40347-2_12

prevalence of pediatric type 1 diabetes in the USA increased from 1.48 to 1.93 per 1000 from 2001 to 2009: when adjusted for completeness of ascertainment, these figures represent a 21.1 % increase (Dabelea et al. 2014). Although it is true that the absolute number of pediatric patients with type 2 diabetes is less than for type 1 diabetes, the rate of increase is greater: the estimated US prevalence increased from 0.34 to 0.46 per 1000 across the same time span, representing a 30.5 % increase (Dabelea et al. 2014).

Now consider a regional example outside the Western world. Close to 20 % of all adults in the world with diabetes live in the Southeast Asia region. As the worldwide figure is estimated to approach 600 million by 2035, the number of people with diabetes in Southeast Asia is estimated to increase to 123 million (International Diabetes Federation 2013). It is extremely concerning from a global public health perspective that most people with diabetes live in low- and middle-income countries; these countries will see the greatest increase over the next two decades (Whiting et al. 2011). The life expectancy of a patient with type 2 diabetes is likely to be reduced by up to 10 years as a result of this condition (Diabetes in the UK Report 2010), a dramatic statistic driven to a large extent by increased risk of heart disease, renal disease, and stroke. Quality as well as quantity of life can also be seriously affected given the additional burdens of nervous system damage, blindness, and lower-limb amputation.

When first-line interventions addressing a patient's dietary and exercise habits have failed to prevent progression to diabetes, initiation of pharmaceutical regimens becomes necessary (an appropriate diet and appropriate levels of exercise should certainly be maintained as adjunctive therapy). At the time of writing this chapter, there are 12 classes of antidiabetic drugs approved in the USA for adults with type 2 diabetes: insulins, biguanides, second-generation sulfonylureas, glinides, thiazolidinediones, α-glucosidase inhibitors, DPP-4 inhibitors, GLP-1 agonists, SGLT2 inhibitors, bile acid sequestrants, dopamine agonists, and amylin analogues. While it may initially appear that this array of currently approved drugs comprises a robust list, the continuing medical need for additional pharmaceutical agents is well captured by the European Medicines Agency's (EMA's) guideline addressing clinical investigation of medicinal products in the treatment or prevention of diabetes, which comments as follows (EMA 2012):

> Glucose control in type 2 diabetes deteriorates progressively over time, and, after failure of diet and exercise alone, needs on average a new intervention with glucose-lowering agents every 3–4 years in order to obtain/retain good control.

That is, a patient's drug regimen becomes insufficient over several years, meaning that an additional drug will be added. When this happens, the drugs the patient is already taking are often kept as they still have a beneficial effect, but their effect alone is not great enough to counteract disease progression. A constant provision of new drugs is therefore needed. Accordingly, it is encouraging to report that new drugs within various classes continue to be developed and that there are multiple new classes of drugs being developed, including PPAR agonists/modulators (PPAR-α agonists, PPAR-δ agonists, PPAR-α/δ agonists, PPAR-δ/γ agonists, PPAR-α/γ co-agonists, and PPAR-α/δ/γ pan-agonists), glucokinase activators, C-C

chemokine receptor type 2 antagonists, IL-1 modulators, G-protein-coupled receptor agonists, apical sodium-dependent bile acid transporter inhibitors, and 11-beta-HSD1 inhibitors (see Mittermayer et al. 2015).

12.1.1 Prospective Exclusion of Unacceptable Cardiovascular Risk for New Antidiabetic Drugs for Type 2 Diabetes

There are multiple aspects of bringing a new antidiabetic drug for type 2 diabetes to market, including safety and efficacy investigations. Of specific interest in this and the following chapter is one component of the overall safety evaluation required by regulators, namely, the prospective exclusion of unacceptable cardiovascular risk associated with the drug. This chapter provides an overview of the genesis of the regulatory landscapes in the USA (FDA 2008) and Europe (EMA 2012) addressing this issue, which were formalized in 2008 and 2012, respectively. Chapter 13 then reviews the requirements of these regulatory landscapes and provides examples of the exoneration of drugs from an unacceptable cardiovascular risk.

12.2 Publication of a Meta-analysis Involving Rosiglitazone

Rosiglitazone is a member of the thiazolidinedione drug class and was approved for marketing by the FDA in 1999 and the EMA in 2000. On May 21, 2007, the *New England Journal of Medicine* e-published a paper entitled "Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes," which was published in the journal in print format on June 14, 2007 (Nissen and Wolski 2007). One result presented in the paper was an odds ratio for myocardial infarction in the rosiglitazone group compared with the control group of 1.43 (95 % CI, 1.03–1.98, $p = 0.03$). This result can be interpreted as follows:

> The result of this meta-analysis is compatible with an increase in risk of myocardial infarction of as little as 3 % and as great at 98 %, and the best estimate is an increase of 43 %.

The fact that the two-sided 95 % confidence interval excludes zero informs us that the result is statistically significant at the 5 % level, and the authors appropriately provided the exact *p*-value as well. This result received considerable attention not only in clinical circles but also in government and media settings.

12.2.1 Details and Critique of the Meta-analysis

In preparing for their meta-analysis, the meta-analysts screened 116 trials, deeming that 48 met their predefined inclusion criteria of employing a randomized comparator group, a similar duration of treatment in all groups, and more than 24 weeks of

drug exposure. Six of the 48 trials did not report myocardial infarctions (or deaths from cardiovascular causes), and therefore their results could not be included in the form of analysis chosen by the authors. Hence, summary statistics from 42 trials were included in this study-level meta-analysis: the combined number of participants was almost 28,000.

Given that the risks of myocardial infarction are low, the odds ratio can be interpreted as a relative risk, which facilitates the following statement: compared with the control treatment group, treatment with rosiglitazone was associated with 1.03–1.98 times the risk of a myocardial infarction. Leaving aside discussion of the analytical methodology chosen for a moment, it is informative to examine the absolute number of events (myocardial infarctions) that went into the analysis. In the rosiglitazone group (totaling approximately 15,600 participants), there were 86 events, and in the comparator group (totaling approximately 12,300 participants), there were 72 events. Making the reasonable assumption that the results for the control group reflect the general background incidence of myocardial infarction in individuals with type 2 diabetes not treated with rosiglitazone, the increase in absolute number of events, 14, is small (Turner and Durham 2009).

Another point that can informatively be made here is the usefulness of presenting statements (best estimates) of absolute risk along with statements of relative risk. Consider the "worst-case scenario" value, in this case provided by the upper limit of the confidence interval presented, i.e., 1.98. Rounding this value up to 2.00 for present purposes, it is meaningful to consider several hypothetical sets of numbers where, in all cases, the risk of some specified event doubles. A given risk could increase as follows: from 1 in 10 to 2 in 10; from 1 in 100 to 2 in 100; from 1 in 1,000 to 2 in 1,000; from 1 in 100,000 to 2 in 1000,000; 1 in a million to 2 in a million; and so on. While the increase in relative risk is mathematically identical in all scenarios, addition of information concerning absolute risk dramatically influences one's perception of the acceptability of a doubling in risk when using that information to make a decision. It is therefore appropriate to communicate a risk by using both relative and absolute statements.

Returning now to the meta-analysis of interest, limitations have been provided by various authors. The meta-analysts themselves noted the following points (Nissen and Wolski 2007):

- The meta-analysts did not have access to the original source data for any of the trials included in the analysis (i.e., they did not have access to participant-level data).
- The meta-analysis pooled the results of a group of trials that were not originally intended to explore cardiovascular outcomes.
- Many of the included trials were small and short term, resulting in few adverse cardiovascular events or deaths. Accordingly, since the results of the analysis were based on a relatively small number of events, the odds ratio "could be affected by small changes in the classification of events."
- Directly related to the previous point, most of the included trials did not utilize centralized adjudication of cardiovascular outcomes (recall discussions in Sect. 6.5), and the definitions of myocardial infarction were not available.

- The confidence interval is wide, "resulting in considerable uncertainty about the magnitude of the observed hazard."

Moreover, they also noted that "a meta-analysis is always considered less convincing than a large prospective trial designed to assess the outcome of interest."Pignone's (2007) commentary on this meta-analysis indicated some of the limitations noted by the authors themselves and also discussed other limitations, including the following:

- The lack of participant-level data limits assessment of the role of important covariates such as age and sex, as well as precluding time-to-event analysis.
- A fixed-effects model was used to combine information from the studies included in the analysis.

With regard to the last bullet point, Pignone provided additional commentary (Pignone 2007):

> A fixed-effects model assumes that all of the trials included drew their participants from the same underlying patient pool, an assumption that is difficult to support. It would have been more appropriate to use a random-effects model, which accounts for both within- and between-study variability. Fixed-effects models usually produce narrower confidence intervals for their summary estimates, which leads to overestimation of the precision of the data.

Diamond and colleagues (2007) expressed this view:

> The meta-analysis was not based on a comprehensive search for all studies that might yield evidence about rosiglitazone's cardiovascular effects. Studies were combined on the basis of a lack of statistical heterogeneity, despite substantial variability in study design and outcome assessment. The meta-analytic approach that was used required the exclusion of studies with zero events in the treatment and control groups. Alternative meta-analytic approaches that use continuity corrections show lower odds ratios that are not statistically significant. We conclude that the risk for diabetic patients taking rosiglitazone is uncertain: Neither increased nor decreased risk is established.

12.3 FDA Advisory Committee Meetings Following the Publication of the Meta-analysis and Their Consequences

Reactions to the publication of the meta-analysis led to the FDA convening a joint meeting of its Endocrinologic and Metabolic Drugs Advisory Committee and its Drug Safety and Risk Management Committee on July 30, 2007, to discuss the cardiovascular ischemic and thrombotic risk of the thiazolidinediones, with a focus on rosiglitazone. (One of this book's authors [JRT] was an invited speaker at the Open Public Hearing session at this meeting: his testimony was that the meta-analysis had been so poorly conducted that no decision-making weight should be afforded to it.) Representatives from rosiglitazone's sponsor and the FDA testified at the meeting. Representatives from the sponsor of another thiazolidinedione, pioglitazone, were invited to attend the meeting, but they did not actively participate.

Two votes were taken by members of the advisory committees. First, they voted 20–3 that rosiglitazone increased the cardiac risk in patients with type 2 diabetes, although many members "made statements accompanying their votes that drew a distinction between the risk as compared with placebo and the risk as compared with other antidiabetic drugs" (Krall 2007). Second, they voted 22–1 that rosiglitazone should not be removed from the market and hence should remain available to patients.

Advisory committee votes are not binding on the FDA, which is therefore free to determine its own course of action. On this occasion the FDA's action was consistent with the members' votes: rosiglitazone was not removed from the market. On November 19, 2007, the FDA announced that the drug's sponsor had agreed to add new information to the existing boxed warning (the text of which concerned heart failure) about a potential increased risk for myocardial ischemic events. Part of the new text read as follows (FDA 2007):

> A meta-analysis of 42 clinical studies (mean duration 6 months; 14,237 patients), most of which compared Avandia to placebo, showed Avandia to be associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction. Three other studies (mean duration 41 months: 14,067 patients), comparing Avandia to some other approved oral antidiabetic agents or placebo, have not confirmed or excluded this risk. In their entirety, the available data on the risk of myocardial ischemia are inconclusive.

In July 2010, the FDA's Endocrinologic and Metabolic Drugs Advisory Committee and its Drug Safety and Risk Management Advisory Committee met jointly again. Compared with the July 2007 meeting, this 2-day meeting had a longer and more complex list of predetermined questions to be voted upon by members. While 12 members voted in favor of removing rosiglitazone from the market, 20 voted against it. Of those 20, 10 voted for additional warnings and restrictions on use of the drug and seven voted for additional warnings. In concordance with these recommendations, FDA did not withdraw rosiglitazone from the US market. However, the drug's sponsor was required to submit a Risk Evaluation and Mitigation Strategy (REMS) within 60 days of the agency's announcement of its decision on September 23, 2010 (Woodcock et al. 2010). The REMS is a tool available to FDA to mitigate overall risk, making the drug available to certain patients under circumstances for which the treatment benefit–risk balance is favorable, while not allowing the drug's use in other patients for whom the benefit–risk balance is likely to be unfavorable. It was introduced in Title IX of the Food and Drug Administration Amendments Act of 2007, which provided the FDA with sweeping new safety authorities. Table 12.1 lists the components of a REMS.

The timetable for submission of assessments is always required, while others are required on a case-by-case basis. Required elements of the rosiglitazone REMS included the following (Sutter and Davis 2010):

- Provision of complete risk information to each patient and documentation in his/her medical record that this information has been received and understood

Table 12.1 REMS components

REMS components
A timetable for the sponsor's submission of assessments
A medication guide
A package insert
A communication plan to health-care providers
Elements to assure safe use (see below)
Individual elements to assure safe use
Health-care providers who prescribe the drug have particular training or experience or are specially certified
Pharmacies, practitioners, or health-care settings that dispense the drug are specially certified
The drug is dispensed to patients only in certain health-care settings, such as hospitals
The drug is dispensed to patients with evidence or other documentation of safe use conditions, such as laboratory test results
Each patient using the drug is subject to certain monitoring
Each patient using the drug is enrolled in a registry

- Documentation from health-care providers that each patient taking rosiglitazone falls into one of two groups:
  1. Patients currently taking rosiglitazone
  2. Other individuals who are not able to achieve glycemic control on other medications and who decide in consultation with their health-care professional not to take pioglitazone (the other thiazolidinedione on the market) for medical reasons
- Documentation from health-care providers that the risk information has been shared with each patient
- Physician, patient, and pharmacist enrolment

The EMA does not have a tool similar to the REMS at its disposal. In contrast to the FDA's decision, and based on the same data and announced on the same day as the FDA's decision, the EMA's Committee for Medicinal Products for Human Use recommended the suspension of the marketing of rosiglitazone in European markets (see Blind et al. 2011), and its marketing authorization is currently suspended.

12.4 Reanalysis of the RECORD Trial and Its Consequences

Three trials conducted by rosiglitazone's sponsor are of relevance in this case study. These are ADOPT (A Diabetes Outcome Progression Trial), the DREAM (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication) trial, and the RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycaemia in Diabetes) trial. Discussions here focus on the RECORD trial, since the FDA's request for subsequent reexamination of this trial had a notable consequence.

At the time that rosiglitazone's sponsor submitted their advisory committee briefing document ahead of the July 2007 FDA Advisory Committee meeting discussed in the previous section, the RECORD trial was ongoing. It was a randomized, open-label, noninferiority trial in type 2 diabetes patients with inadequate blood glucose control on metformin or sulphonylurea alone. As a result of the publication of Nissen and Wolski's (2007) meta-analysis, Home and colleagues (2007) published the results of an unplanned interim analysis on data that were available for 4,447 participants in the trial with a mean follow-up of 3.75 years. These figures translate into 16,675 participant-years of follow-up. At the time that the analysis published by Home and colleagues was conducted, not all events had been adjudicated (recall that this was an unplanned interim analysis). The authors therefore provided results for adjudicated events alone and also for events where adjudication was pending (in which pending events were counted as actual events). In both cases, the results for comparison of acute myocardial infarction between the rosiglitazone and the control group were not statistically significant. Using only adjudicated events, the resulting hazard ratio result was:

- Hazard ratio = 1.16 (95 % CI: 0.75, 1.81)

  This result can be interpreted as follows:

The result from this meta-analysis does not indicate a statistically significant difference in occurrence of myocardial infarction. The result is compatible with an increase as great as 81 % but also with reduction as great as 25 %. Our best estimate is an increase of 16 %.

Addition of pending events increased the hazard ratio somewhat, and the full result was:

- Hazard ratio = 1.23 (95 % CI: 0.81, 1.86)

  This result can be interpreted as follows:

The result from this meta-analysis does not indicate a statistically significant difference in occurrence of myocardial infarction. The result is compatible with an increase as great as 86 % but also with reduction as great as 19 %. Our best estimate is an increase of 23 %.

As can be seen, in each case the lower limit of the two-sided 95 % confidence interval fell below unity (1.00) and the upper limit fell above unity, hence the non-significant result. The Data Monitoring Safety Board for the trial considered all interim analyses and recommended that the trial continue.

In 2010, following their review of rosiglitazone's licensing, the FDA requested a reevaluation of cardiovascular endpoints in the RECORD trial. The methodology used in this review was reported by Lopes and colleagues (2013) and the results were reported by Mahaffey and colleagues (2013). Following their review of the results, on November 15, 2013, the FDA made another announcement, this time expressing "substantially reduced" concern about the risk of myocardial infarction associated with rosiglitazone. The text read as follows (FDA 2013):

The US Food and Drug Administration (FDA) has determined that recent data for rosiglitazone-containing drugs, such as Avandia, Avandamet, Avandaryl, and generics, do not show an increased risk of heart attack compared to the standard type 2 diabetes medicines metformin and sulfonylurea. As a result, we are requiring removal of the prescribing and dispensing restrictions for rosiglitazone medicines that were put in place in 2010. This decision is based on our review of data from a large, long-term clinical trial and is supported by a comprehensive, outside, expert reevaluation of the data conducted by the Duke Clinical Research Institute (DCRI).

FDA continues to evaluate the safety and effectiveness of drugs after they go on the market. In the case of rosiglitazone medicines, previous data from a large, combined analysis of mostly short-term, randomized clinical trials of rosiglitazone had suggested an elevated risk of heart attack, so we required a Risk Evaluation and Mitigation Strategy (REMS), called the Rosiglitazone REMS program. The Rosiglitazone REMS program restricted the use of rosiglitazone medicines to help ensure that their benefits outweighed the risks.

Although some scientific uncertainty about the cardiovascular safety of rosiglitazone medicines still remains, in light of the new reevaluation of the *R*osiglitazone *E*valuated for *C*ardiovascular *O*utcomes and *R*egulation of Glycaemia in *D*iabetes (RECORD) trial, our concern is substantially reduced and the rosiglitazone REMS program requirements will be modified. We are also requiring revisions to the rosiglitazone prescribing information and the patient Medication Guide to include this new information.

Under FDA's proposed modifications to the rosiglitazone REMS program:

- Distribution of the medicines will no longer be restricted. Rosiglitazone may be used along with diet and exercise to improve control of blood sugar in patients with type 2 diabetes mellitus.
- Health-care professionals, pharmacies, and patients will no longer be required to enroll in the rosiglitazone REMS program to be able to prescribe, dispense, or receive rosiglitazone medicines.
- As part of the REMS, health-care professionals who prescribe rosiglitazone medicines will be required to have training about the current state of knowledge concerning the cardiovascular risk of rosiglitazone medicines. Manufacturers will also send Dear Healthcare Provider and Dear Professional Society letters to educate prescribers about the new information.

12.5 FDA Drug Safety Communication in December 2015

A drug safety communication released by FDA on December 16, 2015, went considerably further than their November 2013 statement of "substantially reduced" concern: it read as follows (FDA 2015):

FDA is eliminating the Risk Evaluation and Mitigation Strategy (REMS) for rosiglitazone-containing type 2 diabetes medicines, which are approved as Avandia, Avandamet, Avandaryl, and generics. The REMS is no longer necessary to ensure that the benefits of rosiglitazone medicines outweigh their risks.

In 2013, FDA required removal of the prescribing and dispensing restrictions for rosiglitazone medicines after determining that data did not demonstrate an increased risk of heart attack with rosiglitazone medicines compared to the standard type 2 diabetes medicines metformin and sulfonylurea. FDA also required the drug manufacturers to provide educational training to health-care professionals about the current state of knowledge regarding the heart risks of rosiglitazone medicines. Manufacturers have since fulfilled these requirements. FDA has continued monitoring these medicines and identified no new pertinent safety information. FDA will update the public if any new information becomes available.

12.6 Comment on the "Rosiglitazone Case Study" Before Proceeding to Chap. 13

Given the fact that individuals with diabetes are at higher risk for cardiovascular disease, the intent behind the FDA's and EMA's respective regulatory landscapes addressing the prospective exclusion of unacceptable cardiovascular risk is laudable. However, in the face of the need for a constant supply of new therapeutic agents, this aspect of bringing new antidiabetic drugs to market is considered by many individuals to be excessive. To date, exonerating a drug from an unacceptable cardiovascular risk has typically involved the conduct of a large cardiovascular safety outcome trial. The time, logistical, and financial demands of conducting such trials are enormous, running to perhaps 5–7 years, involving potentially hundreds of investigational sites, and costing hundreds of millions of US dollars. The total cost of all cardiovascular outcome studies conducted to date (as noted in Sect. 12.1.1, examples are discussed in the following chapter) runs well into the billions of US dollars. As Hiatt and colleagues (2013) commented following the reassessment of the RECORD data, "Perhaps the recent experience with rosiglitazone will allow the FDA to become more targeted in its adjudication of the cardiovascular safety of new diabetes drugs, focusing the considerable resources needed to rule out a cardiovascular concern only on drugs with clinical or preclinical justification for that expenditure."

Given the content of FDA's December 16, 2015, drug safety communication, it can reasonably be argued by extension that, at the time of writing this chapter, that regulatory agency thinks that the results presented in the initial publication in this case study (Nissen and Wolski 2007) did not accurately represent the true safety characteristics of rosiglitazone with regard to myocardial infarction. By further extension, it can reasonably be argued that there are currently burdensome regulatory landscapes in the USA and Europe for all new antidiabetic drugs for type 2 diabetes that were driven by a purported increase in cardiovascular (myocardial

infarction) risk that has subsequently been refuted by an influential regulatory agency. That said, at the time of writing this chapter, these regulatory landscapes remain in place and therefore need to be satisfied. Therefore, the following chapter presents the nature of the requirements, examples of how they have been satisfied to date, and pragmatic discussions of new approaches that may allow them to be satisfied more expeditiously in the future.

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Chapter 13

Satisfying the Regulatory Requirements for New Antidiabetic Drugs for Type 2 Diabetes Most Expeditiously

There is considerable interest among many stakeholders regarding ways in which the existing regulatory requirements can be met more efficiently.

13.1 Introduction

The regulatory landscapes for the prospective exclusion of unacceptable cardiovascular risk associated with new antidiabetic drugs for type 2 diabetes in the USA and Europe were formalized in 2008 and 2012, respectively. The FDA's Guidance for Industry specifically addressing this landscape was issued in final format (a rare occurrence) in December 2008 (FDA 2008). The EMA's updated general guidance document addresses this topic. Following the release of a first draft in 2010 and a revised draft in 2011 (a period for public comment followed each release), the document was finalized in May 2012 and became effective in November 2012 (EMA 2012). The first section of this chapter presents the key aspects of each document.

As noted in Chap. 12, at the time of writing this book, the exoneration of a drug from an unacceptable cardiovascular risk has typically involved the conduct of a large, lengthy, and extremely expensive cardiovascular safety outcome trial. There is therefore considerable interest among many stakeholders regarding ways in which the existing regulatory requirements can be met more expeditiously. In January 2015, members of the CSRC published an Expert Perspectives paper entitled "Clinical Development Approaches and Statistical Methodologies to Prospectively Assess the Cardiovascular Risk of New Antidiabetic Therapies for Type 2 Diabetes" that addressed this topic (Geiger et al. 2015). Discussions in this chapter draw from that paper and also cover recent initiatives that are similarly driven.

Geiger and colleagues (2015) deliberately focused on satisfying the regulatory requirements as they are currently written: their paper did not discuss the utility of the safety margins (thresholds) of 1.8 and 1.3 as presented in the FDA Guidance for Industry, or whether every diabetes drug development program should include a cardiovascular outcome trial (see Sager et al. 2015 for related discussions).

J.R. Turner et al., *Cardiovascular Safety in Drug Development and Therapeutic Use*, DOI 10.1007/978-3-319-40347-2_13

13.2 The FDA and EMA Regulatory Landscapes

Before describing these regulatory landscapes, it is important to note that both the FDA and EMA have made it clear that the requirements for prospective exclusion of unacceptable cardiovascular risk do not apply to the development of insulin drugs and insulin analogues. The FDA document notes explicitly that "the absolute deficiency of insulin in patients with type 1 diabetes dictates the need for insulin therapy as an immediate lifesaving treatment for which evaluation of long-term cardiovascular risk may not be practical" (FDA 2008).

13.2.1 The FDA Guidance for Industry

The FDA's Guidance for Industry is entitled "Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes" (FDA 2008). Prior to submission of a New Drug Application (NDA) or Biologics License Application (BLA), sponsors are required to compare the incidence of centrally adjudicated MACE composite endpoint outcomes (recall discussions in Sect. 6.6) occurring in the drug treatment arm with those occurring in the control treatment arm to show that the upper bound of the two-sided 95 % confidence interval for the risk ratio point estimate is less than the 1.8 threshold. This requirement translates to the prospective exclusion of excess cardiovascular risk of 80 % or greater.

This is the first step in what is usually a two-stage process. The requirement can be satisfied by performing a meta-analysis of adjudicated cardiovascular events using participant level data from the Phase II and Phase III trials conducted in the drug's clinical development program or, if the data from the studies included in the meta-analysis will not meet this requirement, by conducting a large cardiovascular safety outcome trial that, alone or when added to the other trials, would discharge the 1.8 threshold.

If the upper bound of the two-sided 95 % confidence interval for the risk ratio point estimate is between 1.3 and 1.8, and the overall benefit–risk analysis supports approval, a postmarketing trial is required to fulfill the second requirement, i.e., definitive demonstration that the upper bound of the two-sided 95 % confidence interval for the risk ratio point estimate is then less than the 1.3 threshold. This requirement translates to the prospective exclusion of excess cardiovascular risk of 30 % or greater. The much larger sample size facilitates greater precision, which translates to a tighter (narrower) confidence interval being placed around the relative risk point estimate, and a greater likelihood, therefore, that the upper bound will be less than the 1.3 threshold. If the upper bound of the two-sided 95 % confidence limit for the risk ratio point estimate from the analysis of preapproval studies is less than 1.3, and the overall benefit–risk analysis supports approval, a postmarketing cardiovascular outcome trial may not be necessary: however, this scenario is likely to occur infrequently.

Although the confidence interval upper limit values are emphasized, the magnitude of the risk ratio point estimate itself will be considered. A detailed statistical

analysis plan addressing proposed analytical strategies for the adjudicated cardiovascular events of interest must be discussed with regulators early in clinical development. If a meta-analysis is planned, it should include all placebo-controlled, add-on, and active-controlled trials performed in the drug's development program.

13.2.2 The EMA Guideline

The EMA's guideline is entitled "Guideline on Clinical Investigation of Medicinal Products in the Treatment or Prevention of Diabetes Mellitus" (EMA 2012). It noted that either of the following should be submitted at the time of the marketing authorization application: an integrated safety analysis focused on adjudicated MACE composite endpoints or results from a long-term, controlled cardiovascular outcome study with at least 18–24 months of follow-up. The guideline did not define any specific thresholds that must be excluded. While emphasis was placed on MACE, MACE-plus can be used as the primary endpoint in certain circumstances. The acceptability of the data will be based on their overall quality and also on the relative risk point estimate and confidence interval obtained for the calculation of cardiovascular risk. Indications of an increased risk in certain adverse events or an unacceptable lack of precision (a wider than desirable confidence interval) may trigger a request for an additional long-term trial to exclude an unacceptable increase in cardiovascular risk.

13.2.3 Rationale for our Focus on the FDA Requirements

Given that the EMA guideline does not include specific thresholds of regulatory interest (i.e., does not provide values analogous to the 1.8 and 1.3 thresholds presented in the FDA guidance), discussions in the rest of this chapter focus on satisfying the explicit FDA thresholds. Nonetheless, many aspects of the discussions are also pertinent to satisfying the EMA guideline's requirements. The clinical implications of the FDA guidance will be discussed first, followed by commentary on statistical considerations. Discussions in this chapter are necessarily a little more complex from a statistical perspective than in other chapters, but we have endeavored to keep them as digestible as possible (recall foundational discussions in Chap. 6).

13.3 Clinical Implications of the FDA Guidance for Industry

The cardiovascular safety outcomes of interest must be defined for all Phase II and Phase III trials, prospectively adjudicated by an independent clinical endpoint committee in a blinded fashion, and analyzed before submission of an NDA or

Table 13.1 Estimated number of cardiovascular events required to discharge the FDA's 1.8 and 1.3 thresholds

	Power		
Threshold	80 %	85 %	90 %
1.8	91	105	122
1.3	456	522	611

BLA. These outcomes must include the components of the MACE composite endpoint. A MACE-plus composite endpoint also including hospitalization for unstable angina or heart failure, coronary revascularizations, or other cardiovascular events may also be employed, depending on the mechanism of action of the drug and/or nonclinical findings.

The number of major cardiovascular events required to show that the upper bound of the two-sided 95 % confidence interval for the estimated risk ratio, or hazard ratio, i.e., the number of events in the drug treatment group divided by number of events in the comparator group, is less than 1.8 preapproval and less than 1.3 postmarketing will depend on the actual true hazard ratio of the new drug relative to comparators. If it is assumed that an investigational antidiabetic therapy is neutral in terms of cardiovascular safety, meaning that the new drug yields neither harm nor benefit (i.e., the hazard ratio is equal to 1.0), approximately 122 and 611 CV events, respectively, would be needed to provide adequate power to discharge the 1.8 and 1.3 thresholds with 90 % power: see Table 13.1.

If the drug affords any cardiovascular protective effect (i.e., the true hazard ratio is less than 1.0), fewer events would be needed to meet the regulatory thresholds. In contrast, if the drug increases the risk of cardiovascular events even slightly (i.e., the true hazard ratio is greater than 1.0), more events would be required to discharge the 1.8 and 1.3 thresholds.

Clinical development plans must take into consideration how to ensure accrual of a sufficient number of adjudicated MACE or MACE-plus outcomes to discharge the 1.8 and 1.3 thresholds and how to provide a meaningful estimate of cardiovascular risk under a variety of potential circumstances. This planning must occur early in development, a time when there may be considerable uncertainty regarding the true effect of the drug on cardiovascular outcomes due to the limited exposure and safety data accumulated at that point. Accomplishing this goal typically requires that sample sizes be increased, that trial durations be extended (beyond the typical 3–6 months, perhaps to a minimum of two years), and/or that study populations be enriched with individuals at higher risk of cardiovascular events: this may include those with relatively advanced diabetes, advanced age, renal impairment, proteinuria, or known cardiovascular disease (Preiss et al. 2011).

Drugs should be tested as monotherapy and in combination with other antidiabetic medications with which they will likely be coadministered in clinical practice. This means that enrichment strategies may only be suitable for select study designs. As an example, participants in a monotherapy trial tend to be younger, have had diabetes for a shorter period of time, have fewer cardiovascular risk factors, and are therefore at lower risk for cardiovascular events. Enrichment in such a trial may be futile. In comparison, participants enrolled in an "add-on to insulin" trial are often older and have

Table 13.2 Impact of sample size and cardiovascular event rate on trial durations at 90 and 80% statistical power

Study duration (years) for 90% power to discharge the 1.3 threshold assuming enrollment at 2,500 participants/year			
	Observed cardiovascular event rate		
Sample size	1%	2%	3%
4000	17	9	6.2
5000	14	7.5	5.3
6000	12	6.5	4.7

Study duration (years) for 80% power to discharge the 1.3 threshold assuming enrollment at 2,500 participants/year			
	Observed cardiovascular event rate		
Sample size	1%	2%	3%
4000	13	6.8	4.8
5000	10.5	5.7	4.1
6000	9	5.1	3.8

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more advanced disease and cardiovascular risk factors. Consequently, enrichment may be more feasible and meaningful in terms of increased cardiovascular event rates.

Chronic kidney disease is a known cardiovascular risk factor. However, certain therapies may not be suitable for investigation in individuals with kidney disease because a reduced glomerular filtration rate may result in accumulation of the drug and/or its metabolites. This limitation may exclude individuals with moderate to severe kidney disease from participating in certain trials, or may necessitate a trial to be conducted solely in these individuals to assess the drug's safety and efficacy in this population.

In addition, it has become accepted (and even expected) that a cardiovascular safety outcome trial be conducted to accrue the number of cardiovascular events to discharge the 1.3 threshold. The approach utilized to discharge the 1.8 and 1.3 thresholds will determine the timing of when this trial will be initiated (during Phase III or post-submission), a topic discussed shortly. Typically, these cardiovascular safety outcome trials are event driven, i.e., they are designed to accrue a prespecified number of outcomes. The number of outcomes will determine the statistical power of the study. The sample size and cardiovascular event rate, contingent on the underlying risk of the population, will impact the duration of the trial, as shown in Table 13.2.

Individuals with type 2 diabetes at high risk of cardiovascular events, e.g., those with established coronary artery disease, multiple cardiovascular risk factors, or recent acute coronary events, are typically enrolled. Although higher-risk individuals are targeted for reasons of efficiency (accruing the needed number of outcomes more quickly), the question has been raised regarding whether or not this is the most appropriate population in which to evaluate the cardiovascular safety of new drugs, given the extent of concomitant medications these patients are usually prescribed and the advanced nature of their underlying cardiovascular disease.

As noted earlier, MACE and MACE-plus composite endpoints are possible candidates for employment in cardiovascular safety outcome trials. MACE is the preferred endpoint [FDA (CDER): Summary review(s) for canagliflozin] because all components are clinically well defined (i.e., they are "hard" endpoints). A MACE-plus composite endpoint may be acceptable in certain circumstances, but the additional cardiovascular events included are often considered more clinically subjective (i.e., they are softer endpoints) and may increase the chance of demonstrating a null effect. Placebo has been the comparator of choice [FDA (CDER). Summary Review for linagliptin] because the cardiovascular safety of existing antidiabetic therapies such as sulfonylureas (Roumie et al. 2012) has been uncertain.

Standard of care for diabetes and cardiovascular risk management should be provided. Retention and adherence are essential to the successful execution of the trial. Follow-up of all participants for the duration of the trial is critical, regardless of whether a participant discontinues study drug, because this is one of the most informative ways to demonstrate the integrity of the study and hence of the data generated.

The cardiovascular safety outcome trial may be designed as a noninferiority trial to demonstrate that the upper bound of the two-sided 95% confidence interval placed around the hazard ratio point estimate is less than 1.3, as a superiority trial to demonstrate that the upper bound is less than 1.0 (and hence that the drug actually reduces cardiovascular risk), or to demonstrate both using a sequential testing methodology.

13.4 Approaches to Satisfy the 1.8 and 1.3 Safety Margins

At the time of writing this chapter, it is approximately 7 years since the release of the FDA's December 2008 Guidance for Industry in this domain. Sponsors have commonly used meta-analyses of cardiovascular events from Phase II and Phase III trials, a cardiovascular safety outcome trial, or some combination thereof to discharge the FDA's 1.8 and 1.3 thresholds. These approaches are reviewed in turn.

13.4.1 Meta-analysis and a Cardiovascular Safety Outcome Trial

A validated approach to discharge the 1.8 and 1.3 thresholds has been to conduct a meta-analysis of MACE or MACE-plus outcomes accrued during Phase II and Phase III trials to discharge the 1.8 threshold and to conduct a cardiovascular safety outcome trial to discharge the 1.3 threshold. The outcome trial might begin during Phase III, after submission of a marketing approval request, or post-approval. If the trial is initiated during Phase III, interim data from the study may or may not be included in the meta-analysis to discharge the 1.8 pre-submission requirement.

13.4.2 Meta-analysis of Cardiovascular Events from Phase II and Phase III Trials to Discharge the 1.8 Threshold and a Cardiovascular Safety Outcome Trial to Discharge the 1.3 Threshold

Saxagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, was approved by the FDA in 2009, shortly after the FDA's 2008 guidance was issued. Centralized adjudication of cardiovascular events had not been a requirement during the drug's development period. Instead, to assess the cardiovascular safety of the drug, meta-analyses using reported cardiovascular Medical Dictionary for Regulatory Activities (MedDRA) event terms were conducted. Post-approval, the SAVOR-TIMI 53 trial (Scirica et al. 2014) was conducted to demonstrate that the upper bound of the two-sided 95 % confidence interval placed around the hazard ratio was less than 1.3.

A total of 16,492 participants with type 2 diabetes or at risk for cardiovascular events were randomized to saxagliptin or placebo (on a background of standard of care for diabetes and cardiovascular risk factors) and followed for a median of 2.1 years. The primary endpoint was occurrence of MACE outcomes. A primary endpoint event occurred in 613 participants in the saxagliptin group and in 609 participants in the placebo group. The statistical analysis plan prespecified that a test for noninferiority would be conducted first, followed by a test for superiority. Saxagliptin did not increase or decrease the rate of MACE outcomes (hazard ratio = 1.00, 95 % CI = 0.89–1.12: $p < 0.001$ for noninferiority, $p = 0.99$ for superiority).

Dapagliflozin, a sodium glucose co-transporter 2 (SGLT-2) inhibitor, was approved by the FDA in 2014. The sponsor planned two sequential meta-analyses to discharge the 1.8 threshold (Sponsor's Background Document, Dapagliflozin). The first meta-analysis was to occur after a prespecified number of studies completed, and, if the 1.8 threshold was not discharged, a second meta-analysis was to be conducted after another group of studies concluded. Given the plan for sequential testing, alpha spending modifications were specified to preserve the type 1 error rate. The first meta-analysis was performed on 78 MACE-plus outcomes from 6,228 participants in 14 trials. The hazard ratio for dapagliflozin vs. comparator (placebo and active comparators combined) was 0.67 (95 % CI: 0.42, 1.08). Thus, an unacceptable increase in cardiovascular risk in participants with type 2 diabetes was ruled out, and the second meta-analysis was not necessary.

This approach provided two opportunities to discharge the 1.8 threshold, with the possibility of an earlier submission if the first meta-analysis did so successfully. The DECLARE-TIMI 58 trial was a superiority trial designed to test the hypothesis that dapagliflozin reduces the incidence of MACE events compared with placebo in individuals with type 2 diabetes at high risk for cardiovascular events. The study was also designed to definitively exclude an unacceptable cardiovascular risk from dapagliflozin in these individuals, i.e., to demonstrate a post-approval upper bound of the two-sided 95 % confidence interval placed around the hazard ratio point estimate of less than 1.3 to further support the cardiovascular safety of dapagliflozin.

13.4.3 Meta-analysis Inclusive of Interim Data from a Cardiovascular Safety Outcome Trial to Discharge the 1.8 Threshold and a Cardiovascular Safety Outcome Trial to Discharge the 1.3 Threshold

Canagliflozin, a SGLT-2 inhibitor, was approved by the FDA in 2013. The strategy employed to discharge the 1.8 safety margin was to perform a meta-analysis using MACE-plus events from the Phase II and Phase III trials and interim data from the Canagliflozin Cardiovascular Assessment Study (CANVAS) (CANVAS: Canagliflozin Cardiovascular Assessment Study 2015). CANVAS was designed to demonstrate that treatment with canagliflozin would reduce cardiovascular risk (based on MACE events) compared with placebo in participants with type 2 diabetes with, or at high risk for, cardiovascular events. The trial was designed to enroll two sequential cohorts, with a decision to recruit further participants dependent upon a protocol-specified interim analysis of results from the initial cohort (Cohort A). An interim analysis by an independent data monitoring committee was planned to be conducted 4 years after trial initiation to assess study feasibility of achieving the primary hypothesis of cardiovascular benefit and to recommend that study recruitment be reopened if the interim results were positive. The data monitoring committee operated under a prespecified interim monitoring program whereby they could recommend early termination for safety (ruling out a 30 % or greater excess cardiovascular risk) or for futility. If enrollment was not reopened, participants in Cohort A would continue to be followed for long-term safety.

The plan was to perform a meta-analysis to discharge the 1.8 threshold when 201 MACE-plus outcomes had accumulated in the development program. Assuming an annualized event rate of 2.5 % in the CANVAS trial, approximately 160 MACE-plus outcomes were expected within 2 years of activating Cohort A, which would provide more than 90 % power to discharge the 1.8 threshold. These data would be included in a submission dossier prepared by a group of researchers who were independent of the team that would continue to manage the trial. Cohort A would continue to generate additional events that could be combined with events from Cohort B to discharge the 1.3 threshold if Cohort B were activated. Data from both cohorts would be combined and the trial would continue until a maximum of 1,600 MACE outcomes had accumulated, which would provide 90 % power to detect a 15 % cardiovascular risk reduction. Given that the maximum number of MACE outcomes from Cohort A and the maximum number of outcomes from combining Cohort A and Cohort B were both prespecified, and no results from either cohort would be publicly available during the course of the entire CANVAS trial, this study design was considered statistically valid and free of bias.

A group sequential approach was planned to discharge the 1.3 threshold. The significance levels for the multiple analyses were based on the Lan–DeMets spending function with an O'Brien–Fleming boundary. The first analysis to discharge it would be conducted at the time when the meta-analysis to discharge the 1.8 threshold was performed. The next planned interim meta-analysis would be conducted when approximately 500 MACE-plus events had accrued, and a final interim analysis was planned to occur after approximately 700 events had accumulated, if the 1.3

threshold had not yet been discharged. In actuality, Cohort A enrolled 4,411 participants within 15 months, and a decision was taken not to activate Cohort B.

When 201 MACE-plus events had accrued from 9,632 participants enrolled in nine trials, the meta-analysis showed that canagliflozin did not unacceptably increase MACE-plus events based on a hazard ratio point estimate of 0.91 (95 % CI: 0.68–1.22) (FDA Medical review document). However, evaluation of the individual components of the MACE-plus composite endpoint revealed that the hazard ratio point estimate for nonfatal stroke was 1.46 (95 % CI: 0.83, 2.58). Also, the CANVAS trial contributed the majority of events in the meta-analysis (nearly 80 %) due to its size and higher cardiovascular risk population. Therefore, data from CANVAS were analyzed separately from the other studies. For CANVAS, the hazard ratio point estimate was 1.0 (upper bound of the two-sided 95 % CI = 1.39) compared with 0.65 (upper bound of the two-sided 95 % CI = 1.21) in the other 8 trials. Given the relatively low number of cardiovascular events, it is not surprising that the observed hazard ratio point estimates for each analysis lay above and below 1.0 with fairly wide confidence intervals.

13.4.4 Single Cardiovascular Safety Outcome Trial to Discharge Both the 1.8 and 1.3 Thresholds

A single cardiovascular safety outcome trial initiated during Phase III could be used to discharge both the 1.8 and 1.3 thresholds. The trial would be designed to demonstrate a post-approval upper bound of the two-sided 95 % confidence interval placed around the hazard ratio point estimate of less than 1.3 to provide evidence of the drug's cardiovascular safety. The primary intent would be to show that the new therapy does not increase the risk of MACE or MACE-plus events. The trial could be designed as a noninferiority trial, a superiority trial, or both using a sequential testing methodology. Interim data (MACE or MACE-plus outcomes) could be used to discharge the 1.8 threshold, and these data could be included in the submission dossier. Alternatively, interim data from the cardiovascular safety outcome trial could be combined with MACE or MACE-plus events collected in Phase II and Phase III trials in a meta-analysis to discharge the 1.3 threshold.

Alogliptin, a DPP-4 inhibitor, was approved by the FDA in 2013. For this program, a single cardiovascular safety outcome trial, Examination of Cardiovascular Outcomes with Alogliptin (EXAMINE), was used to discharge both the 1.8 and 1.3 thresholds. EXAMINE was a noninferiority trial with a prespecified noninferiority margin of 1.3, using a MACE primary endpoint (White et al. 2013). A total of 5,380 participants with type 2 diabetes and having had an acute myocardial infarction or unstable angina requiring hospitalization were randomized to either alogliptin or placebo in addition to existing antidiabetic and cardiovascular therapies and followed for 40 months. Four interim analyses of the MACE endpoint were prospectively planned using an O'Brien–Fleming alpha spending function. If, at any of these analyses, the 1.8 threshold was not discharged, the trial would be stopped for futility. If at a given analysis the 1.8 threshold was discharged, the trial would continue and an interim analysis would be performed after 550 and 650 events accrued to discharge the 1.3 threshold. If noninferiority was declared and the

conditional power for superiority (with 650 events) was less than 20 % at the 550-event interim analysis, the study would be terminated.

After 83 MACE events had accrued, the first interim analysis was performed and the upper bound of the confidence interval placed around the hazard ratio point estimate was 1.51. An independent statistician performed this analysis and communicated the results to the independent data monitoring committee. Having therefore discharged the 1.8 threshold, the sponsor was able to include these interim results in the NDA. To protect trial integrity and statistical validity, the researchers involved with this analysis were not involved in subsequent trial conduct, data reviews, and trial analyses and did not communicate with those still involved in the study.

In keeping with the statistical plan, the next interim analysis of MACE events was performed after 550 events had occurred, resulting in a hazard ratio point estimate of 0.96 and an associated confidence interval upper bound of 1.17, demonstrating that alogliptin was noninferior but not superior to placebo. Since the conditional power to show superiority with 650 events was less than 20 %, the trial was terminated. Prior to data lock, an additional 71 participants had a primary endpoint event. The final analysis of MACE yielded a hazard ratio of 0.96 and an associated confidence interval upper bound of 1.16 ($p<0.001$ for noninferiority; $p=0.32$ for superiority), confirming that alogliptin did not unacceptably increase cardiovascular risk.

13.5 Statistical Considerations

In addition to the need to ensure accrual of a sufficient number of cardiovascular events, there are a number of statistical issues that need to be addressed with regard to meeting the FDA requirements. Several of these were not included in the FDA guidance but have since emerged in various forums (Geiger et al. 2015). First, a statistical analysis plan must be created early in development that describes how both the 1.8 and the 1.3 thresholds will be discharged. While separate alpha spending functions for each margin are acceptable, repeated testing for 1.8 and/or 1.3 requires alpha adjustment (Sahlroot 2012). Although the guidance discusses risk ratio estimates, it is the hazard ratio estimated from the Cox proportional hazards model that is being referred to (see Cox 1972). Thus, the terms risk ratio and hazard ratio may be used interchangeably. The hazard ratio estimates required for demonstrating noninferiority in a meta-analysis should be obtained using the stratified version of the Cox proportional hazards model. If these estimates are adjusted for covariates, these covariates must be specified in the statistical analysis plan.

13.5.1 Meta-analysis and Heterogeneity

If a meta-analysis of MACE or MACE-plus events from Phase II and Phase III trials is conducted, all placebo-controlled, add-on, and active-controlled trials should be included, as previously noted. However, these trials will likely vary in size, duration,

participant characteristics including baseline cardiovascular risk, and comparator therapies. These differences may lead to heterogeneity, i.e., dissimilarities in results that may or may not be due to chance. Heterogeneity has been observed in some of the cardiovascular meta-analyses submitted to the FDA (Sahlroot 2012). Utilization of similar study designs, eligibility criteria, and a uniform process to collect and adjudicate cardiovascular events may mitigate some of this risk. The quality of the meta-analysis will depend on the quality and comparability of the component trials and the methodological rigor employed in conducting the meta-analysis.

If study participants are at low to moderate cardiovascular risk, it is possible that a small number of cardiovascular events may be reported in a given trial. In this case, the precision of the hazard ratio point estimate for the new drug vs. the comparator may be low, as indicated by large confidence intervals. If the true hazard ratio is close to 1.0, it can be expected that point estimates greater and smaller than 1.0 will be observed among the trials. Therefore, it is recommended that all of the hazard ratios and their associated confidence intervals for each study included in the meta-analysis be displayed in a forest plot, accompanied by an interaction test for a common hazard ratio.

Whether or not to include trials with no cardiovascular events in a meta-analysis has been a highly debated topic. If a trial had a sufficiently long period of follow-up and no cardiovascular events were reported, these data would appear to support the hypothesis of noninferiority; however, no formal statistical method exists for estimating the cardiovascular risk from such data, and they are typically excluded from the analysis. Tian and colleagues (2009) discussed a method of obtaining an exact confidence interval for the difference in event rates at a fixed time point that permits combining data from trials that have zero events with data from other trials. This method could be utilized as a supportive sensitivity analysis.

Prior to issuance of the FDA guidance, the cardiovascular safety of many antidiabetic therapies had not been established and, for some classes of drugs, concern still exists that they may increase cardiovascular risk (Horsdal et al. 2011; Schramm et al. 2011; Phung et al. 2013). Hence, comparisons of cardiovascular event rates with the new drug vs. placebo and active control groups combined are challenging to interpret. Therefore, meta-analyses of the investigational drug vs. placebo only and then vs. active comparators only should be considered and may be requested by some regulatory authorities.

13.5.2 Adaptive Methodologies

Adaptive methodologies, such as sample size or outcome re-estimations and early stopping decision rules, could be specified in the statistical analysis plans for cardiovascular safety outcome trials, potentially to reduce study duration, increase the chances of success, and facilitate earlier submissions. Many different types of adaptive designs are in use. The most common adaptation is to increase the sample size if the rate at which outcomes are accruing is slow. This modification raises no statistical issues if done in a blinded manner.

More recently, there has been interest in adaptive designs where the sample size and number of events are increased based on an unblinded look at interim analysis results. For example, a trial might be initially sized based on the number of MACE outcomes needed to demonstrate noninferiority; however, if superiority appears likely based on the conditional power available at the time of an interim analysis, the number of needed MACE outcomes and the sample size could be increased. Such adaptive designs require special statistical analyses to protect the alpha level and special provisions to minimize operational bias (FDA 2010). This approach reduces the risks to participants (and to the sponsor) associated with initiating a large superiority trial up-front, when there is limited information about the compound.

Group sequential designs permit interim monitoring of accumulating data with the possibility of stopping early for efficacy, safety concerns, or futility. Cardiovascular safety outcome trials typically require a substantial follow-up time to obtain the required number of cardiovascular events and are therefore attractive candidates for group sequential monitoring. The number of planned interim analyses and the cumulative number of cardiovascular events at which each interim analysis is performed in a group sequential design study should be specified in the study's statistical analysis plan to promote trial integrity and ensure adequate documentation of testing procedures. At each interim analysis, a determination is made as to whether or not there is sufficient evidence to stop the trial and demonstrate noninferiority by performing an hypothesis test, or equivalently by computing a confidence interval that is adjusted for multiple looks at (analyses of) the accumulating data.

The first interim analysis should occur only after a reasonable number of events have occurred, and there has been adequate participant exposure to the drug to be able to draw a meaningful clinical conclusion. In practice, it may not be feasible to adhere strictly to the planned spacing and number of interim analyses. For example, the actual number of events at an interim analysis after the data are cleaned and the database locked may differ from that specified in the statistical analysis plan. For this reason, an alpha spending function (Lan and DeMets 1983) must be specified that controls the overall type 1 error rate while allowing flexibility with respect to the number and timing of interim analyses. Because of this flexibility, most group sequential designs utilize spending functions from families such as the O'Brien–Fleming family (O'Brien and Fleming 1979) and the Pocock family (Pocock 1977) to elicit stopping boundaries at interim looks, rather than specifying the stopping boundaries directly.

Spending functions differ in how aggressively they spend alpha relative to the timing of each interim analysis. The selection of a spending function is not prescriptive, but the criteria should include the ability to have a convincing point estimate and sufficient information to address secondary hypotheses and other safety considerations adequately if the study is terminated early to declare success. The Lan and DeMets (1983) O'Brien–Fleming-type spending function, which is often preferred, meets these criteria because very little alpha is spent in early looks. This spending function produces group sequential boundaries that are very similar, but not

identical, to the O'Brien–Fleming boundaries. If the trial is stopped early, the evidence is compelling due to their higher hurdle. In addition, the penalty for the interim analysis is minor, resulting in a sample size that is approximately equivalent to that employed in a fixed study design of the same power.

In contrast, a Lan and DeMets (1983) Pocock-type spending function spends alpha more aggressively. This spending function produces group sequential boundaries that are very similar, but not identical, to the Pocock boundaries. This function increases the likelihood of stopping early relative to the Lan and DeMets O'Brien–Fleming-type spending function, but the penalty for the more aggressive alpha spending is the requirement for a larger maximum number of events to maintain the same power. Due to the lower interim hurdle, the estimate of reduction in cardiovascular risk for a trial that stops early, while sufficient to claim statistical significance, might not be sufficiently convincing to alter medical practice.

13.5.3 Restricted Mean Survival Time Analysis

The hazard ratio provides a convenient summary of the difference between two survival distributions. Its estimate from the Cox proportional hazards model has some attractive statistical properties including the incorporation of covariate effects, efficient testing of the null hypothesis that the hazard ratio =1.0, and group sequential monitoring. For noninferiority cardiovascular outcome trials, however, it has some drawbacks. It lacks interpretability as a clinical measure of patient outcomes. For example, it does not easily translate into lives saved or lost. Also, the implication of ruling out a hazard ratio greater than 1.3 depends on the background hazard rate. A 30 % increase in the hazard rate is less of a cause for concern if the background hazard rate is low than if it is high. Moreover, the hazard ratio often changes over time, in which case its interpretability is questionable. Furthermore, the variance of the hazard ratio estimate depends mainly on the observed number of cardiovascular events and does not utilize information about participant follow-up. Thus, for cardiovascular safety outcome trials, which are typically characterized by low event rates, the hazard ratio confidence interval is rather wide, resulting in extremely large trials or long follow-up durations to rule out excess risk, as seen previously in Table 13.2.

Uno and colleagues (Uno et al. 2015) discussed these drawbacks in connection with some recently completed trials and suggested alternative measures that might be more suitable for safety studies. An attractive measure for quantifying the underlying differences between groups for a time-to-event endpoint is the restricted mean survival time (RMST) (Royston and Parmar 2011; Zhao et al. 2012). The RMST is the population average of the amount of event-free survival time experienced during T months of follow-up. For a cardiovascular safety outcome trial, the RMST provides an easy, clinically meaningful interpretation regarding the average time to a MACE outcome during the T months of follow-up for participants assigned to the drug treatment arm compared with the control treatment arm. The RMST can be

estimated by the area under the corresponding Kaplan–Meier survival curve up to time T. Thus, unlike the hazard ratio, it does not require various assumptions to be made, and the precision of this estimate takes into consideration both the number of events and the participant exposure in the analysis. As a result, the difference of two RMSTs may be a more robust and sensitive metric for detecting a safety signal in a cardiovascular safety outcome trial.

Uno and colleagues (2015) reconstructed data from the SAVOR-TIMI 53 cardiovascular safety outcome trial of saxagliptin (Scirica et al. 2013) to illustrate the greater efficiency and interpretability of the RMST measure over the hazard ratio for demonstrating cardiovascular safety. By repeated random selection of a subset of individuals, using fixed proportions of 15, 20, and 25 % of the original study size, they obtained very tight confidence intervals for RMST differences. For example, with only 2,474 patients (15 % of original sample size), it would have been possible to claim with 95 % confidence that the average time to a MACE event in the saxagliptin group was within ±12 days of the average time to a MACE event in the placebo group, through 900 days of patient follow-up. Therefore, if a difference of 12 days out of 900 days could be considered a clinically meaningful margin of noninferiority, the saxagliptin trial could have demonstrated safety with substantially fewer participants.

13.6 Points to Consider

There are pros and cons to consider for each of the approaches used to date to satisfy the 1.8 and 1.3 thresholds. Points for consideration include the following:

- If only one meta-analysis of cardiovascular events from Phase II and Phase III trials is planned, there is the possibility that fewer events may accrue in the program than projected. This may result in failure to discharge the 1.8 threshold, depending on the effect of the drug on cardiovascular outcomes. One way to mitigate against this is to specify plans for sequential meta-analyses with appropriate alpha adjustment in the statistical analysis plan, as exemplified in the dapagliflozin program. Simulations using various assumptions (e.g., differing cardiovascular event rates and study durations) may aid in these planning efforts.
- If a meta-analysis includes cardiovascular events from Phase II and Phase III trials and interim results from an ongoing cardiovascular safety outcome trial, there is a high probability that a sufficient number of cardiovascular events will accrue to discharge the 1.8 threshold. However, the results may be influenced by the events from the outcome trial because, due to its design and the nature of the population under study, the majority of events in the meta-analysis will likely come from this single trial. Moreover, heterogeneity may be introduced into the meta-analysis due to differences in the baseline cardiovascular risk. It is also possible that meta-analysis of events solely from the cardiovascular outcome trial may yield differing results from those of a meta-analysis of events from the Phase II and Phase III trials. Although the totality of evidence must be considered

in the interpretation of the drug's effect on cardiovascular risk, the findings from trials with higher-risk participants cannot be ignored and may make interpretation of the point estimate and confidence intervals more challenging.

- Use of a group sequential design for a cardiovascular safety outcome trial with specified interim analyses can be quite advantageous, as exemplified by the EXAMINE trial. It can offer multiple opportunities to discharge the 1.8 threshold, the 1.3 threshold, or both, to terminate the trial for futility, or to terminate if there is insufficient evidence of superiority, thereby reducing the trial's duration, participant exposure, and costs. However, these designs require significant up-front planning and resources. Trial simulations based on a range of assumptions (e.g., differing risk ratios and cardiovascular event rates) can be useful in developing the optimal design.
- The primary composite endpoint (MACE or MACE-plus) and the patient population (high or low cardiovascular risk) may influence the point estimates and confidence intervals. For example, individuals with type 2 diabetes and high cardiovascular risk may represent only a fraction of the population intended to use the drug upon marketing approval. Use of cardiovascular event data solely from such individuals may or may not be indicative of the drug's cardiovascular effects in lower risk populations.

13.6.1 Confidentiality of Interim Results from Cardiovascular Safety Outcome Trials

One topic that has recently emerged and warrants discussion is the issue surrounding maintenance of confidentiality of interim results from an ongoing cardiovascular safety outcome trial. As noted previously, interim analysis can be specified in the statistical analysis plan for an outcome study, and some sponsors have included interim results in meta-analyses intended to discharge the 1.8 threshold. Doing this requires extensive up-front planning. Firewalls must be implemented to maintain the confidentiality and integrity of the ongoing study after the interim analysis has been performed. This also means that the individual(s) involved in the meta-analysis must not be involved whatsoever in the conduct of the ongoing study. Sponsors were able to include interim results from ongoing dedicated outcome trials in support of approval of alogliptin and empagliflozin. However, another sponsor's efforts to do the same resulted in a different outcome. The sponsor withdrew the NDA purportedly based on discussions with the FDA about how the interim data would be reviewed and resubmitted the NDA when the cardiovascular safety outcome trial had completed (Sanofi 2014).

In 2014, the FDA hosted a public hearing on the confidentiality of interim results in cardiovascular safety outcome trials to gather input from various stakeholders on this topic. The issue of preserving the integrity of the ongoing trial extends beyond sponsors to include regulators, who are challenged by this scenario because they must provide sufficient information to physicians and patients to use a drug that is

now on the market (i.e., regulators need to be transparent when they approve a drug). Hence the key question deliberated at this forum was the following: When a trial to evaluate cardiovascular safety of a new treatment is ongoing at the time a drug is approved, and where results from the trial contribute to the approval decision, does disclosure of detailed analysis (such as hazard ratio point estimates and their associated confidence intervals) undermine the integrity of the ongoing trial and jeopardize its continuation, potentially eliminating or substantially delaying regulators' ability to obtain needed long-term safety information? While many viewpoints were expressed and solutions proposed, it was unanimously agreed that the interim results must remain confidential. Moreover, it was recognized that this is a balancing act, balancing the need to get effective therapies to patients as quickly as possible without jeopardizing the question of interest, i.e., the cardiovascular safety of the drug, which necessitates completion of the ongoing cardiovascular outcome trial. The need for global regulatory cooperation to maintain the confidentiality of interim data also was emphasized as sponsors submit NDAs/BLAs worldwide.

13.7 Emerging Challenges

As of writing this chapter, five cardiovascular safety outcome trials in patients with type 2 diabetes have reported results, as shown in Table 13.3.

Four of the trials, evaluating three DPP-4 inhibitors and one GLP-1 receptor agonist, showed that the drug did not increase or decrease the incidence of MACE or MACE-plus outcomes. In the most recently reported trial, the EMPA-REG Outcome Trial (Zinman et al. 2015), empagliflozin was shown to statistically significantly reduce cardiovascular risk by 14 % in participants with type 2 diabetes with established cardiovascular disease compared with placebo, a first for a new antidiabetic therapy. This was driven by a significant reduction in death (all-cause mortality or cardiovascular death; $p < 0.001$ for each) as there were no between-group differences for myocardial infarction or stroke.

The findings from the EMPA-REG Outcome Trial are very exciting for patients with type 2 diabetes and may alter clinical practice guidelines. Nonetheless, the study results also raised a number of questions. For example, was the cardiovascular benefit observed with empagliflozin specific to this drug, or is this a drug class effect? The results from the other ongoing SGLT-2 inhibitor outcome trials will answer this question. Will placebo remain the comparator of choice since there is now an antidiabetic therapy with compelling evidence that it reduces cardiovascular risk in patients with type 2 diabetes? How might product labeling be impacted? Will the results of a single trial support an indication for cardiovascular risk reduction?

As of writing this chapter, a considerable number of other cardiovascular outcome studies are ongoing, and examples are provided in Table 13.4. A wealth of data will continue to amass from these studies. However, the focus to date has been on the MACE composite outcome, and the question has been raised as to whether

Table 13.3 Completed cardiovascular safety outcome trials in participants with type 2 diabetes

Study	N	Population	Follow-up	Intervention	Primary endpoint	Primary outcome (HR and 95 % CI)
DPP-4 inhibitors						
SAVOR-TIMI 53 (Scirica et al. 2013)	16,492	T2DM with history of or at risk for CV event, HbA1c 6.5–12 %	Median 2.1 years	Saxagliptin vs. placebo	MACE	HR = 1.00 (0.89, 1.12)
EXAMINE (White et al. 2013)	5,380	T2D with ACS in 15–90 days before randomization, HbA1c 6.5–11 %	Median 18 months	Alogliptin vs. placebo	MACE	HR = 0.96 (upper bound ≤1.16)
TECOS (Green et al. 2015)	14,671	T2D, established CVD, HbA1c 6.5–8 %, 1–2 oral antidiabetic agents	Median 3.0 years	Sitagliptin vs. placebo	MACE +	HR = 0.98 (0.88, 1.09)
GLP-1 receptor agonist						
ELIXA (Pfeffer et al. 2015)	6068	T2D with ACS 180 days before screening	Median 25 months	Lixisenatide vs. placebo	MACE+	HR = 1.02 (0.89, 1.17)
SGLT-2 inhibitor						
EMPA-REG outcome (Zinman et al. 2015)	7020	T2D with history of CV disease, HbA1c ≥7–10 %	Median 3.1 years	Empagliflozin vs. placebo	MACE	HR = 0.86 (0.74, 0.99)

Abbreviations: *ACS* acute coronary syndrome, *CI* confidence interval, *CV* cardiovascular, *HbA1c* glycated hemoglobin, *HR* hazard ratio, *T2D* type 2 diabetes

Table 13.4 Ongoing cardiovascular outcome studies in participants with type 2 diabetes at the time of writing

Study	N	Intervention	Primary endpoint	Start/estimated completion date	ClinicalTrials.gov identifier
DPP-4 inhibitors					
CAROLINA	6000	Linagliptin vs. glimepiride	MACE+	OCT 2010/SEP 2018	NCT01243424
CARMELINA	8000	Linagliptin vs. placebo	MACE+	JUL 2013/JAN 2018	NCT01897532
Omarigliptin study	4202	Omarigliptin vs. placebo	MACE+	OCT 2012/DEC 2020	NCT01703208
GLP-1 receptor agonists					
LEADER	9340	Liraglutide vs. placebo	MACE	AUG 2010/NOV 2015	NCT01179048
EXSCEL	14,000	Exenatide QW vs. placebo	MACE	JUN 2010/APR 2018	NCT01144338
REWIND	9622	Dulaglutide vs. placebo	MACE	JUL 2011/APR 2019	NCT01394952
SUSTAIN™ 6	3297	Semaglutide vs. placebo	MACE	FEB 2013/JAN 2016	NCT01720446
ITCA-650	4000	ITCA-650 (exenatide in DUROS) vs. placebo	MACE+	MAR 2013/JUL 2018	NCT01455896
Albiglutide study	9400	Albiglutide vs. placebo	MACE	JUL 2015/MAY 2019	NCT02465515
SGLT-2 inhibitors					
CANVAS	4411	Canagliflozin vs. placebo	MACE	DEC 2009/JUN 2017	NCT01032629
CREDENCE	3700	Canagliflozin vs. placebo	Secondary endpoint: MACE+	FEB 2014/JAN 2020	NCT02065791
DECLARE-TIMI 58	17,276	Dapagliflozin vs. placebo	MACE	APR 2013/APR 2019	NCT01730534
Ertugliflozin study	3900	Ertugliflozin vs. placebo	MACE	NOV 2013/MAR 2021	NCT01986881
Insulin regimens					
DEVOTE	7673	Insulin degludec vs. insulin glargine	MACE	OCT 2013/SEP 2016	NCT01959529
Other therapies					
TOSCA IT	3371	Add-on pioglitazone vs. add-on sulphonylurea	All-cause mortality, nonfatal myocardial infarction, nonfatal stroke, or unplanned coronary revascularization	SEP 2008/DEC 2018	NCT00700856

this is the most appropriate endpoint. Heart failure is a common occurrence in diabetic patients and several older antidiabetic therapies have increased the risk for heart failure. This has led some to propose that a more systematic evaluation of hospitalization for heart failure be undertaken (McMurray et al. 2014), either as a primary endpoint event or a key secondary endpoint. Contributing to this notion is the fact that several studies have raised questions regarding the effect of newer drugs on heart failure risk. In the SAVOR-TIMI 53 trial, saxagliptin was associated with an increased risk for heart failure hospitalization (3.5 % vs. 2.8 %, $p = 0.007$) (Scirica et al. 2013; Scirica et al. 2014). However, an increased risk was not observed with alogliptin (White et al. 2013; Zannad et al. 2015) or sitagliptin (Green et al. 2015), and a 35 % reduction in hospitalization for heart failure was observed in patients treated with empagliflozin ($p = 0.002$) (Zinman et al. 2015). Therefore, are we currently employing the "correct" endpoints to answer the cardiovascular safety question of interest for new therapies? Are we studying the correct populations and how generalizable are the current findings to low cardiovascular risk patients? Answering these important safety questions necessitates continued dialogue in the scientific and regulatory communities.

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Part VI
Additional Considerations in General Drug Safety and Therapeutic Use

Chapter 14

Postmarketing Cardiovascular Safety Considerations

The approval decision does not represent a singular moment of clarity about the risks and benefits associated with a drug – preapproval clinical trials do not obviate continuing formal evaluations after approval (Institute of Medicine of the National Academies 2007).

14.1 Introduction

The fundamental importance of safety assessments has been emphasized many times in previous chapters. We have discussed "engineering safety" into new molecular entities, safety evaluations in nonclinical studies, and safety evaluations in preapproval clinical trials. While data collected in preapproval investigations and clinical trials are clearly very important, it is appropriate here to acknowledge that they have limitations. With regard to preapproval clinical research, Olsson and Meyboom (2006, p. 229) commented as follows:

> The randomized controlled clinical trial is the method of choice for the objective and quantitative demonstration of the efficacy and tolerability of a new medicine. Nonetheless, such studies have limitations in discovering possible adverse events that may occur, in particular those that are rare or develop after prolonged use, in combination with other drugs, or perhaps due to unidentified risk factors. Clinical trials are inherently limited in duration and number of patients, and, significantly, patients are selected prior to inclusion. In other words, the conditions of a trial are artificial compared with the real-life use after the introduction of a medicine.

Given our focus on preapproval randomized clinical trials to date, these statements may initially sound somewhat surprising. However, they are true. The strength of preapproval randomized clinical trials is that they are comparative, not necessarily representative (see Senn, 2007): they are essential to the process of new drug development, but evaluation of a drug must not stop once marketing approval has been granted. As the Institute of Medicine of the National Academies (2007) observed, "The approval decision does not represent a singular moment of clarity about the risks and benefits associated with a drug – preapproval clinical trials do

J.R. Turner et al., *Cardiovascular Safety in Drug Development and Therapeutic Use*, DOI 10.1007/978-3-319-40347-2_14

not obviate continuing formal evaluations after approval." The necessity for both pre- and post-approval clinical investigations is captured in the term lifecycle clinical development.

Useful information in the postmarketing realm can be gathered in various ways. One way is via therapeutic use (Phase IV) clinical trials. Other avenues come from the realm of clinical practice. In clinical practice, individuals are not participants in a clinical trial who have been randomized to one of the trial's treatment arms: prescribing physicians make treatment decisions with each of their patients on a case-by-case basis such that each individual receives an active treatment (an approved pharmaceutical agent) that, to the best of physician's knowledge, has a favorable benefit–risk balance for that individual. Important information about a drug's safety and efficacy (now termed effectiveness) can be gathered in a non-randomized manner by collecting data in various ways discussed in this chapter.

Another topic addressed in this chapter concerns the extent to which a drug's labeling, initially predicated on preapproval data but certainly modifiable in due course based on the collection of compelling postmarketing data, is heeded by prescribing physicians. Clinical pharmacists who are part of a clinical team working in an inpatient setting are well placed to look for physicians' prescribing decisions that may not be in accordance with information in a drug's label and therefore carry a degree of unwanted proarrhythmic risk.

At the end of the chapter, we consider the pharmacologic treatment of drug-induced QT prolongation and *torsades*. While we hope that these drug-induced outcomes occur as infrequently as possible, it is appropriate to consider the actions that should be taken when they do occur.

14.2 Limitations of Preapproval Clinical Trials

From a drug safety perspective, one key issue in drug development is the (very) low probability of observing (very) rare adverse events in preapproval clinical trials, even in large therapeutic confirmatory trials. Such side effects are probabilistically much more likely to surface once the drug is widely used, and unfortunately some of these side effects may be extremely serious. The "rule of threes" is instructive here (Strom 2005). The number of individuals participating in a clinical trial that would be needed to be 95 % confident that a single case of an identified adverse event of interest would be seen is approximately three times the reciprocal of the frequency of the event in the general population. That is, for an event that occurs in 1/1,000 individuals, a sample size of 3,000 subjects would provide 95 % confidence of observing at least one event. For adverse events that are considerably more rare (e.g., rhabdomyolysis, *torsades*), much larger sample sizes would be needed (e.g., 30,000 and 300,000 for events with frequencies of 1/10,000 and 1/100,000, respectively). Trials of this magnitude are infeasible from

both cost and time perspectives. Cobert (2007, p. 11–12) commented on this phenomenon as follows:

> Should the [adverse drug reaction] be dramatic and rapidly discovered, such as torsades de pointes, aplastic anemia, or rhabdomyolysis, there will be a torrent of recriminations about why this was not discovered earlier during the [preapproval] clinical testing. The correct response is that the testing of only 5,000 to 10,000 patients could not pick up such a rare event. This response is usually lost in the clamor.

Therapeutic use clinical trials and postmarketing surveillance therefore play critical roles in cardiovascular drug safety and indeed in many other domains of drug safety.

A second issue concerns the fact that preapproval clinical trials typically employ relatively homogeneous participant samples. For example, potential participants who have other illnesses or medical conditions, including renal and hepatic impairment, are typically excluded, as are those taking (at least certain) concomitant medications. Additionally, the age range of participants can be fairly limited. A third issue concerns the length of time that a patient may take the new drug: for chronic diseases this is likely to be (very) much longer than the treatment period in preapproval clinical trials. The long-term safety of a drug that is suitable for chronic administration is therefore not fully known at the time that the drug is approved. Fourthly, and of particular salience for certain drug classes, its propensity for abuse is not known, nor is the likelihood that patients will develop a dependency on the drug (some of the discussions in the following chapter touch upon this issue).

Another important point concerns how drugs are actually taken by patients. Howren (2013) observed as follows:

> Adherence is a term used to describe the extent to which an individual's behavior coincides with health-related instructions or recommendations given by a health care provider in the context of a specific disease or disorder. The term has been used extensively in psychology and medicine in reference to acute, chronic, and preventive treatment regimens (e.g., a course of prescribed medication, wound self-care), preventive health screenings, dietary restrictions, exercise recommendations, and other health behaviors.

While the negative effects of patient nonadherence have been known for decades (Howran 2013) and authoritative sources such as the World Health Organization and the American Heart Association put average nonadherence among those with chronic diseases around 50–75 %, the literature still reveals a predominance of discussions of, and further research into, the problem rather than offering immediate action plans (Turner 2013). This topic is addressed in the following chapter in Sect. 15.6.

14.3 Therapeutic Use Trials

Therapeutic use trials are conducted once a drug is on the market. They may be optional studies or studies required by a regulatory agency as a condition of approving the drug for marketing. In the former case, the biopharmaceutical company sponsoring a trial may wish to know more about the drug's performance in

individuals who were not well represented in preapproval trials, e.g., those with compromised liver function and/or taking several concomitant medications. Other sponsors, such as an institute within the National Institutes of Health, may wish to explore a drug's place in future treatment guidelines, and hence conduct trials comparing its safety and/or effectiveness with other treatment options. Therapeutic use trials can be experimental or nonexperimental, nomenclature that is explained in the respective following sections.

14.3.1 Experimental Therapeutic Use Trials

The term experimental means that researchers are systematically facilitating the administration of the drug of interest to some individuals and a control drug to others: the preapproval therapeutic exploratory and therapeutic confirmatory trials discussed in previous chapters were experimental in nature.

Consider here three examples of therapeutic trials from the domain of antihypertensive medications: the Systolic Hypertension in the Elderly Program (SHEP) trial (The Systolic Hypertension in the Elderly Program (SHEP) Cooperative Research Group 1988; SHEP Cooperative Research Group 1991), the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (ALLHAT Collaborative Research Group 2000), and the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial (Jamerson et al. 2008).

While each of these was a therapeutic use randomized clinical trial, the designs of the trials differed such that the most appropriate control treatment was employed in each case to best answer the research question of interest (Turner and Hoofwijk 2013). SHEP was a multicenter, randomized, double-blind, placebo-controlled trial of chlorthalidone for isolated systolic hypertension. ALLHAT employed a multicenter, randomized, double-blind, active-controlled design to compare chlorthalidone with each of three alternative antihypertensive treatments with regard to the incidence of nonfatal myocardial infarction and fatal coronary heart disease in hypertensive patients with at least one other risk factor for coronary heart disease. ACCOMPLISH was also a multicenter, randomized, double-blind, active-controlled clinical trial, but one that differed from ALLHAT in that a combination therapy comprising benazepril plus amlodipine was compared with benazepril plus hydrochlorothiazide with regard to reduction of cardiovascular events in high-risk hypertensive patients (Turner and Hoofwijk 2013).

14.3.2 Nonexperimental Therapeutic Use Trials

The term nonexperimental simply means that researchers are not systematically facilitating the administration of the drug of interest to some individuals and a

control drug to others. The inclusion of "non" in the term nonexperimental is not pejorative (Turner 2010): it simply means that, in contrast to a randomized clinical trial, the study design is not an experimental one. These studies are often called observational studies. However, that terminology is not the most descriptive or distinguishing, since observations are also made during randomized clinical trials. The term nonexperimental is arguably preferable since it simply reflects that a controlled intervention is not made by the researchers.

One example of a nonexperimental study is the cohort study. A cohort study is a nonexperimental study that collects information from an identified group of individuals in an overall population, such as those receiving the marketed drug of interest (see Gamble 2014). Other study designs include case-control studies, cross-sectional studies, and ecological studies. Case reports and case series can also be informative.

14.4 Pharmacovigilance

While various definitions can be found in the literature, Man and Andrews (2002, p. xvii) regarded pharmacovigilance to be "the study of the safety of marketed drugs under the practical conditions of clinical usage in large populations." Shakir and Layton (2002) provided a more encompassing definition that also included preapproval monitoring, detection, and evaluation of drug safety hazards. Stephens (2004, p. 2) provided a comprehensive list of the aims of pharmacovigilance:

- Identification and quantification of previously unrecognized adverse drug reactions
- Identification of patient subgroups at particular risk of adverse drug reactions (e.g., the risk being related to dose, age, sex, and underlying disease)
- Continued monitoring of a drug's safety throughout the duration of its use to ensure that its risks remain acceptable when considered in conjunction with its benefits
- Comparison with the adverse drug reaction profiles of drugs within the same therapeutic class
- Further elucidation of a drug's pharmacological/toxicological properties and the mechanisms of action that lead to adverse drug reactions
- Detection of significant drug–drug interactions between new drugs and cotherapy with agents already on the market
- Communication of appropriate information to health professionals

14.5 Pharmacoepidemiology

Strom (2005, p. 3) defined pharmacoepidemiology as "the study of the use of and the effects of drugs in large numbers of people." Dimensions of interest include safety, effectiveness, utilization, and cost. Going back to randomized clinical trials

for a moment to allow a subsequent comment to be put into context, Matthews (1999, p. i) made the following comment at the turn of the millennium:

> Over the last two to three decades, randomised concurrently controlled clinical trials have become established as the method which investigators must use to asses new treatments if their claims are to find widespread acceptance. The methodology underpinning these trials is firmly based in statistical theory, and the success of randomised clinical trials perhaps constitutes the greatest achievement of statistics in the second half of the twentieth century.

At the time that quote was published, it is likely fair to say that the statistical methodologies available to the discipline of pharmacoepidemiology were less well developed than for randomized clinical trials. In a paper published 8 years later entitled "In defense of pharmacoepidemiology--embracing the yin and yang of drug research," Avorn (2007) commented as follows:

> We forget how difficult it was to establish the rules of the road for conducting randomized trials. In terms of design theory and public policy, drug-epidemiology is now where randomized trials were in the 1950s. We have much to learn about methods, transparency, and protecting the public's interest. But that work can be done, and we often have no other way of gathering vital information.

In the last decade, tremendous advances have been made: see Consiglio et al. (2013), Hennessy and Strom (2015), and Hennessy et al. (2016).

14.6 Postmarketing Surveillance

The terms used in the previous two sections, pharmacovigilance and pharmacoepidemiology, would probably both be suitable to reflect the discussions in this section. The term postmarketing surveillance has been chosen since it makes clear that our focus here is squarely in the post-approval domain.

Postmarketing surveillance involves surveillance for occurrences that have been identified in advance as potential safety concerns and also for unanticipated events. Regulatory agencies may approve a drug based on their belief at the time of approval that the benefit–risk balance is favorable, but also make it clear to the drug's sponsor that their assessment of the benefit–risk balance's favorability could change if certain adverse events suggested in preapproval trials materialize to a concerning degree during postmarketing surveillance.

14.6.1 Spontaneous Reporting

In multiple countries, health-care professionals are encouraged to report adverse drug reactions spontaneously to the drug's sponsor, the appropriate governmental health agency, or a third party. In some countries, including the USA, Canada, and

the UK, patients are similarly encouraged to do so. Cobert (2007, p. 12) commented that this practice "depends on the good will and energy of nurses, pharmacists, physicians, and consumers" to report adverse drug reactions. Given that health-care professionals and patients lead busy lives, the simple reality is that other systems of information collection are also of great importance.

14.6.2 Active Postmarketing Surveillance

It has become clear that active postmarketing surveillance can provide critical drug safety information. This is "an idea whose time has come," but it is actually over four decades since the forerunner of modern approaches was utilized. Pioneering work was done at the University of Southampton, United Kingdom. Inman (1981a, b) and Inman et al. (1986) was instrumental in founding prescription-event monitoring (PEM). PEM studies are prospective cohort studies. Inman's goal was to recruit the first 10,000 patients who received a new drug with the goal of identifying any adverse drug reaction occurring in more than 1 in 1,000 patients.

14.7 Registries

In the previous chapter, we discussed the large cardiovascular safety outcome trials that are currently required for the prospective exclusion of unacceptable cardiovascular risk associated with new antidiabetic drugs for type 2 diabetes. There is currently considerable interest in alternative ways of exonerating a drug (see Sager et al. 2015): however, these methodologies can also be applicable in other therapeutic categories.

14.7.1 A De Novo Prospective Registry/Observational Study

This method of evaluation is one in which all patients who are prescribed the drug of interest once it has received marketing approval are enrolled in a prospective, unblinded, non-randomized, observational study. Because limited data collection is involved and data are collected via minimal patient contact, this approach provides a cost-effective mechanism to gather information on the endpoint of interest.

Major limitations of this type of study are the lack of a control group to estimate background cardiovascular risk and potential selection bias as it relates to which patients are prescribed the drug. The study design can therefore be greatly strengthened by incorporating a comparator group.

14.7.2 A Prospective Registry/Observational Study Built on an Existing Registry Platform

A prospective registry study adds additional but somewhat limited data collection requirements to an existing registry. For example, it might be of interest to make a request for a new data field for patient exposure to a drug of interest to the National Cardiovascular Data Registry (NCDR), a registry active among over 2,000 cardiologists and more than 2,200 hospitals and 700 practices (NCDR 2016). This database is already in use by regulators for postmarketing assessment and, at times, it is also used as a platform for clinical trials.

The addition of supplementary data collection activities is a highly cost-efficient strategy compared with conducting a cardiovascular safety outcome study. However, like all registries, the utility of this strategy is constrained by methodological concerns. Continuing with the example of the NCDR, since this registry is deployed only to cardiologists, any cardiovascular safety signals would be gathered only for those patients who are referred for cardiovascular care. Therefore, it would not provide adequate information if the registry were intended to capture the incidence of cardiovascular events for a widely prescribed noncardiovascular drug. Additionally, there may be practical constraints, including institutional review board concerns and technical aspects surrounding data access and integration.

14.7.3 A Prospective Registry/Observational Study Built on an Electronic Health Record Platform

The emergence of electronic health record (EHR) technologies, also referred to as electronic medical records, may facilitate the development of cost-effective strategies to evaluate drug safety following marketing approval. EHR platforms potentially offer the advantage of standardized, ongoing, consecutive data capture that involves clinical practice settings, more representative patient populations than those participating in preapproval trials, much greater sample sizes, and a reduced data entry burden. Additional benefits include that patients can potentially be matched with control patients using different clinical factors such as comorbidities, concurrent medications, and demographics. However, while this technology is rapidly evolving, current challenges include the lack of acceptable EHR study methodologies for cardiovascular safety assessments and practical and technical issues such as intra-operability and research process models.

14.7.4 A Retrospective Analysis Built from Data Warehouses

The emergence of “Big Data” from accountable care organizations and large-scale medical centers offers the promise of ascertainment of true incident rates predicated

on the power of statistical modeling from extremely large databases. One of the best examples of this structure is the Mini-Sentinel Initiative (discussed in further detail in Sect. 14.7.6), a distributed database model that currently includes health information on approximately 125 million persons (FDA 2016a).

Data come from insurance claims and administrative databases, including outpatient dispensing codes, inpatient and outpatient diagnoses, and procedural codes. Theoretically, therefore, Mini-Sentinel should be able to provide the number of exposed lives as well as outcome information that will permit assessment of cardiovascular event incidence with high statistical fidelity in a cost-effective manner. Mini-Sentinel has active project teams for statistical method development, identification of health outcomes, and validation of health outcomes. While the distributed nature of the approach currently limits the number of searches and the ability to assess potential safety issues in a more real-time manner, the EHR approach may be able to provide similar capabilities in a non-distributed manner in the future (Sager et al. 2015).

14.7.5 Relative Strengths and Weaknesses of These Methodologies Compared with a Prospective Randomized Cardiovascular Outcome Study

As in many areas of drug development and therapeutic use, different methodologies to collect information have relative strengths and weaknesses, and when two or more are candidates for use in a certain circumstance, these characteristics must be evaluated and the better option chosen. Consider first their weaknesses. Compared with prospective, randomized cardiovascular safety outcome studies, they are less rigorously performed as they are nearly always non-blinded and non-randomized. Therefore, there can be considerable heterogeneity among different observational databases.

The strengths of these potential alternate approaches include that they may be able to provide information that likely cannot be obtained from a cardiovascular safety outcome study in certain cases, e.g., when event rates are so low that there are serious practical concerns surrounding the feasibility and/or completion of the study. These approaches are less resource intensive than cardiovascular safety outcome studies, and, therefore, they have the potential to provide both regulators and the public with information about cardiovascular safety in a rapid manner without placing an undue burden on the sponsors developing the drugs of interest (Sager et al. 2015).

14.7.6 The Sentinel Initiative, the Science of Safety, and Mini-Sentinel

In May 2008 the FDA released a report entitled “The Sentinel Initiative: National Strategy for Medical Product Safety” (FDA 2016b). The report started with a

message from then Commissioner Dr. Andrew von Eschenbach, the first part of which read as follows:

> Imagine a national electronic safety system capable of tracking the performance of a drug or medical product, beginning with the earliest stages of clinical research through its effects on millions of Americans who use it to treat or to recover from an illness or condition.
>
> The US Food and Drug Administration of the twenty-first century needs such an electronic system to serve as *sentinel* over the safety of medical products and help FDA fulfill its responsibility to protect the health and well-being of the American people. Accurate and reliable information must be obtained before products are approved and afterwards when they are being used by large and diverse populations.

The goal of the Sentinel Initiative was described as being to create a national, integrated, electronic system for monitoring medical product safety. The report also introduced the emerging science of safety, a science that combines "a growing understanding of disease and its origins with new methods of safety and signal detection" (FDA 2016b). Updates have been provided by various authors, including the following: Platt et al. (2012), Robb et al. (2012), Ball et al. (2016), and Chakravarty et al. (2016).

14.8 Evidence-Based Medicine

Evidence-based medicine was defined by Sackett and colleagues (1996) as follows:

> Evidence-based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research. By individual clinical expertise we mean the proficiency and judgment that individual clinicians acquire through clinical experience and clinical practice. Increased expertise is reflected in many ways, but especially in more effective and efficient diagnosis and in the more thoughtful identification and compassionate use of individual patients' predicaments, rights, and preferences in making clinical decisions about their care.

There are two components to evidence-based medicine and two related sets of responsibilities. The first component is clinical research. Clinical research is a scientific endeavor that provides evidence concerning potential therapeutic interventions. Once clinical trials have been conducted, results are published in appropriate peer-reviewed journals. Everyone involved in clinical research has the responsibility to provide the best possible evidence in this manner (a topic discussed in the following chapter with particular attention to safety results).

The second component of evidence-based medicine is clinical practice. Clinicians have the responsibility of providing the best possible care to each of their individual

patients. One part of being able to provide this optimum care is remaining aware of pertinent evidence that is published in clinical communications (no small task given the enormous amount of publications per year). It is also incumbent on clinicians to be able to decide for themselves if the evidence presented in a clinical communication is solid evidence and if the conclusion conveyed by the publication is justified based on the results presented. As Katz (2001, p. xvi) commented:

> Part of the burden for the responsible cultivation of higher standards and better outcomes in medicine falls, naturally, to researchers and those who screen and publish their findings. But application is ultimately the responsibility of the clinician, who is obligated to consider not only the pertinence of particular evidence to his or her practice, but also the adequacy and reliability of the evidence itself.

Therefore, an appreciation of study design, experimental methodology, statistical analysis, and clinical interpretation is vital for clinicians who must decide whether the evidence presented in journal publications is adequate and reliable and therefore constitutes an appropriate basis for clinical care.

14.8.1 Scientific Evidence and Clinical Judgment

In addition to remaining abreast of journal publications and evaluating the scientific validity of their results and interpretations, a clinician also has to use clinical judgment in providing clinical care. As we have noted, the evidence from a clinical trial is not perfectly generalizable to the target population with the disease or condition of interest. Therefore, a clinician is constantly faced with the task of deciding to what extent the information from a given clinical trial applies to a particular patient. As Katz (2001, pp. xi, xvii) observed:

> If our patient is older than, younger than, sicker than, healthier than, ethnically different from, taller, shorter, simply different from the subjects of a study, do the results pertain? … No degree of evidence will fully chart the expanse of idiosyncrasy in human health and disease. Thus, to work skillfully with evidence is to acknowledge its limits. All of the art and all of the science of medicine depends on how artfully and scientifically we as practitioners reach our decisions. The art of clinical decision making is judgment, an even more difficult concept to grapple with than evidence.

14.9 Inappropriate Prescriptions of QT-prolonging Drugs and Opportunities for Clinical Pharmacists to Reduce Them

When making prescribing decisions, physicians consider safety at the individual patient level, utilizing labeling information in their clinical decision-making process. When assessing the benefit–risk balance of prescribing the same drug to different patients, various factors may make the benefit–risk balance favorable in one

case and unfavorable in another. That is, based on the information (evidence) presented in a drug's label regarding QT prolongation liability and a variety of clinical factors unique to individual patients, physicians make a clinical judgment concerning whether or not to prescribe a QT-prolonging drug. As just noted in the quote presented from Katz (2001, pp. xi, xvii), judgment is a complex issue.

Prescribing decisions are made at the discretion of the physician making them. It is certainly possible for caring and highly informed physicians to make individual decisions that may seem at odds with labeling information in cases where the physician believes that doing so serves a patient's best interests. This is true not only in the present context of QT-prolonging drugs but in many other therapeutic areas. Consider the case of antihypertensive medication. Treatment of hypertensive patients can be quite complex, and, accordingly, there are many practice guidelines and scientific statements addressing this issue (Turner and Kothari 2014; Weber et al. 2014; White et al. 2014). There are certainly many hypertension specialists who are extremely conversant with prescribing guidelines, communicate very well with their patients, and sometimes may recommend treatment that differs from the guidelines because, for certain patients, they genuinely believe that such action is warranted. Such action is certainly within the spirit of guidelines, which make clear the importance of a physician's expertise and clinical experience. However, the literature reveals that deviation from guideline-recommended treatment is not always as considered (Turner 2013).

A key question in the current context is this: How well do prescribing physicians pay attention to drug labeling information regarding QT prolongation liability? Several studies provide a less-than-encouraging answer. Consider the following three examples.

Tisdale and colleagues (2012) studied the prevalence of QTc prolongation in patients admitted to cardiac units in a large urban academic medical center in the USA and the frequency of administering QT-prolonging drugs to patients presenting with QTc prolongation. Of 251 patients admitted during a 1-year period already displaying QTc interval prolongation, 34.7 % were subsequently administered QT-prolonging drugs. Of 166 patients admitted with a QTc interval >500 msec, 42.2 % were subsequently administered QT-prolonging drugs. In more than half of these patients, additional QTc interval prolongation ≥60 msec occurred. The authors concluded that QTc prolongation is common among patients admitted to cardiac units, and QT-prolonging drugs are commonly prescribed to them.

Franchi and colleagues (2016) evaluated the prevalence of prescribing QT-prolonging drugs at hospital admission and discharge and the risk factors associated with their use in patients aged 65 years and older. Among 3,906 patients prescribed at least one drug at admission, 55.2 % were taking at least one QT-prolonging drug. Risk factors independently associated with the use of any QT-prolonging drugs were increasing age, multi-morbidity, hypokalemia, atrial fibrillation, and heart failure. The authors concluded that, despite their risks, QT-prolonging drugs are widely prescribed to hospitalized older persons.

Michels and colleagues (2016) reported the first study involving patients with life-threatening cardiac arrhythmias associated with drug-induced QT prolongation

admitted as emergency cases to a medical intensive care unit. Of 33 identified cases, 55 % presented with *torsades* with the need of resuscitation. Cardiac QT-prolonging drugs were reported in 24 % of the cases, and the other 76 % involved noncardiac medications. The authors concluded that physicians should be aware of QT-prolonging drugs and able to identify patients at risk and avoid specific drugs in such patients.

It should be emphasized here that occurrences of drug-induced *torsades* typically require multiple contributing factors to be present at the same time. These clinical risk factors include female sex, structural heart disease, metabolic and electrolyte abnormalities, bradycardia, increased drug exposure, and inherited syndromes causing QT prolongation (Vlachos et al. 2016). Concomitant medications lead to the possibility of drug–drug interactions and exacerbation of overall proarrhythmic liability. Physicians who are considering prescription of a drug with acknowledged QTc prolongation liability for a given patient should therefore take into account the patient's full profile before prescribing the drug.

Given their expert knowledge of pharmacology and extensive knowledge of information concerning drug-induced QT prolongation and/or *torsades* that is included in drug labels, pharmacists can play an important role in reviewing prescribing decisions and alerting physicians in cases where reassessment seems advisable. Clinical pharmacists in both dispensing and non-dispensing roles within hospital systems typically have access to patient information (e.g., labs, orders, doctors' notes) that allows them to assess the appropriateness of a given pharmacotherapeutic decision in a thorough manner. Pharmacists in other important roles (e.g., those working in a retail setting) who are concerned by the prescription of a drug or drug regimen with QTc prolongation liability may not have access to the patient's full profile, but alerting the prescribing physician is still a judicious action.

It should be acknowledged that the fact that a given decision is changed per se does not necessarily mean that an adverse cardiac reaction to the drug originally prescribed was prevented: by definition, we will never actually know whether an adverse outcome would have resulted. Nonetheless, it is a reasonable expectation that the occurrence of multiple potentially harmful decisions being successfully changed to reflect approved regulatory labeling stands to reduce cumulative totals of adverse outcomes (Dhanani et al. 2016).

14.10 Recognition of QTc Prolongation in Clinical Practice

Another key question in the context of present discussions is this: How well do physicians in clinical practice read ECGs, with a particular focus on the identification of QTc prolongation? Going back one step, it is also informative to ask the same question with regard to medical students, since they will become practicing physicians in due course. Consider the following examples.

Lever and colleagues (2009) assessed the skills of final year medical students ($n = 52$) and resident medical (house) officers ($n = 50$) in New Zealand with regard to recognizing and interpreting common or life-threatening ECG abnormalities. The

participants in the study were given 15 ECG strips to interpret in a 30-min period: 14 of the strips contained a characteristic component that would be identified if the students and medical officers read the ECG correctly, and one strip showed normal sinus rhythm and no abnormalities. The results were not encouraging. Accurate heart rate determination was highly variable. When inaccurate readings were made, they tended to underestimate heart rate by 10–20 bpm. Thirty-four percent of readers reported that an abnormality was present when interpreting the normal ECG strip. Of particular relevance to present discussions is that ECG strip # 12 had "sinus rhythm with long QT interval and repolarisation abnormalities." QT prolongation was accurately interpreted by only 7 % of readers "despite the fact that the strip contained 'marked abnormalities'" (Lever et al. 2009).

Kopeć and colleagues (2015) surveyed Polish medical students in the clinical years of their training (years 4–6), with students in their preclinical training (years 1–3) acting as controls. The authors concluded that the clinical students' ability "to recognize ECG signs of emergencies and common heart abnormalities is low …Our results indicate qualitative and quantitative deficiencies in teaching ECG interpretation at medical school" (Kopeć et al. 2015).

Al-Khatib and colleagues (2005) assessed the ability of health-care practitioners to measure the QT interval correctly and "to identify factors and medications that may increase the risk of QT interval prolongation and torsades de pointes." The survey was an anonymous, self-administered questionnaire that contained 20 questions about the QT interval. Just over 500 individuals completed the survey: less than half (43 %) measured the QT interval correctly. The authors concluded as follows:

> The majority of health care practitioners cannot correctly measure the QT interval and cannot correctly identify factors and medications that can prolong the QT interval. Our findings suggest that greater attention to the QT interval is warranted to ensure safer use of QT prolonging medications.

Moving to a more recent publication, consider the study reported by Choo and colleagues (2014). Their study aimed to assess prescribing physicians' monitoring for arrhythmic risk with drugs prolonging the QT interval. All inpatients over a 6-month period who were under the care of cardiologists and general physicians at a hospital in the UK and were prescribed drugs with known risk of *torsades* (LQT drugs) were identified. Of the 4,133 patients admitted during the study period, 234 (6 %) patients were prescribed an LQT drug. Of these, 100 (43 %) were prescribed the drug by cardiologists, and 134 (57 %) were prescribed the drug by a general physician. Of those admitted with a preexisting prescription for an LQT drug, an ECG was performed in 167 (96 %) of patients, and QTc prolongation was identified in 59 (34 %). Of those who received a new prescription for an LQT drug, 23 (38 %) had QTc prolongation, and more patients under the care of a cardiologist had a repeat ECG within 48 h than patients under the care of a general physician (84 % vs. 11 %, respectively). QTc prolongation was only recognized in six (14 %) and two (5 %) patients under the care of a cardiologist and a general physician, respectively. The authors concluded that recognition of drug-induced QT prolongation was poor and that education of prescribers and an electronic prescribing system may be beneficial (Choo et al. 2014).

14.11 Publication Bias?

Given all the work by sponsors and regulators that goes into the creation of QT-prolonging information in drug labels, it is a little disconcerting to read study reports such as those cited in the previous sections. Additional thoughts are therefore presented here.

Piantadosi (2005, pp. 582–583) defined publication bias as a "tendency for studies with positive results, namely those finding significant differences, to be published in journals in preference to those with negative findings." For biopharmaceutical clinical trials, the term positive typically refers to a study reporting a statistically significantly greater magnitude of therapeutic benefit (efficacy) than the control treatment, and the term negative refers to a study in which the test drug does not do so. Bowers and colleagues (2006) observed that publication bias can result from other influences in addition to journal editors simply tending to favor positive studies. One of these is that some studies that fail to show positive results are never submitted for journal publication since the trials' sponsors regard the results as unfavorable. From the perspective of the greater good, defined very simply here as patients' health, this can be a very unfortunate outcome.

Imagine a scenario in which a sponsor obtains compelling evidence from a therapeutic confirmatory (Phase III trial) that a new drug is ineffective. Imagine also that the drug is the first in a new class of drugs for which a Phase III trial has been completed. Multiple sponsors may have development programs planned for another drug in the same class. If they were to read a journal publication in which the first sponsor reported compelling evidence that their drug was not effective, other sponsors may reconsider their scheduled investments in their own development programs for a similar drug. The worst-case scenario here is that multiple sponsors spend large sums of money on development programs that, truth be told, are unlikely to produce an effective drug: patients would be much better served by that time and financial costs being channeled into development plans for other drugs that are more likely to reach marketing approval and hence provide therapeutic benefit to patients.

Consider now the topics discussed in the preceding section and whether publication bias may be responsible for the disconcerting message portrayed by the examples cited. In a study evaluating physicians' ability to read ECGs accurately, including the identification of QTc prolongation, would journal editors be interested in publishing submitted manuscripts whose conclusions are "Physicians are very good at what they should be very good at"? Similarly, would they be interested in manuscripts providing results saying "Physicians are very good at paying attention to QTc prolongation information in drug labels, something that they should be very good at"? Such manuscripts would lack the sensationalism (if sometimes muted) of manuscripts concluding that doctors are not very good at executing tasks for which they should be thoroughly trained and at which they should excel. May it therefore be the case that reports saying that physicians cannot read ECGs adequately, and reports that physicians do not pay enough attention to drug warning labels, get preferential consideration for publication?

Two other possibilities exist, of course. One is that researchers who examine physicians' performance and find it to be exemplary may not write and then submit manuscripts, and so the only manuscripts that are eligible for publication are those reporting poor performance. The other possibility (and one that is considerably more disconcerting) is that every study that has been conducted has found poor performance. We do not presume to have the answers to these questions: we simply raise them for readers' consideration.

14.12 Treatment of Drug-Induced QT Prolongation and *Torsades*

In 2006, the American College of Cardiology (ACC), American Heart Association (AHA), and European Society for Cardiology published guidelines for the management of ventricular arrhythmias, including drug-induced *torsades* (Zipes et al. 2006). The key recommendations were endorsed in a 2010 statement from the ACC and AHA (Drew et al. 2010). More recently, Thomas and Behr (2016) discussed management strategies for drug-induced QT prolongation and *torsades*: the summary in the following section is based on their paper.

To put some of the strategies discussed in context, it should be recalled that occurrences of drug-induced *torsades* typically require multiple contributing factors to be present at the same time. Some of these clinical risk factors include female sex, structural heart disease, metabolic and electrolyte abnormalities, bradycardia and pauses, increased concentrations of "culprit" drugs, and inherited syndromes causing QT prolongation (Vlachos et al. 2016). Concomitant medications lead to the possibility of drug–drug interactions and exacerbation of overall proarrhythmic liability.

14.12.1 QT Prolongation Without Observed Episodes of Torsades

Consider first patients with clinically important QT prolongation in the absence of observed episodes of *torsades*. If feasible, the responsible drug(s) should be discontinued and other modifiable risk factors addressed. These include correction of oxygen saturation and plasma potassium, calcium, and magnesium concentrations as necessary. Patients should undergo continuous 12-lead ECG monitoring, and the QT interval should be evaluated periodically, with the frequency depending on the clinical circumstances and the extent of QT prolongation.

14.12.2 Torsades

As for occurrences of isolated QT prolongation, the responsible drug(s) should be discontinued if feasible and modifiable risk factors addressed, including hypoxia,

hypokalemia, and hypomagnesemia. Several sources recommend that serum potassium should be maintained in the high normal range (4.5–5.0 mmol/l), although evidence is limited (Zipes et al. 2006; Drew et al. 2010).

Prolonged episodes of continuous *torsades* associated with severe hypotension or cardiac arrest should be terminated by electrical cardioversion (Drew et al. 2010). However, it is more typical for *torsades* to occur in recurrent, self-terminating bursts. In these cases, treatment is directed at two outcomes: stabilizing the myocardium using magnesium sulfate and shortening repolarization by increasing heart rate using chronotropic drugs such as isoproterenol or cardiac pacing (Zipes et al. 2006).

Administration of magnesium sulfate is currently recommended as immediate first-line treatment for *torsades* (Zipes et al. 2006). While the mechanism of action is uncertain, magnesium may reduce the amplitude of early after-depolarizations by inhibiting the late influx of calcium ions via L-type calcium channels that are associated with delayed ventricular repolarization. Consequently, early after-depolarizations are less likely to reach threshold potential and provoke or sustain *torsades* (Kaye and O'Sullivan 2002).

Isoproterenol increases heart rate due to nonselective β_1/β_2-adrenoceptor agonist actions, thereby shortening the QT interval and the effective refractory period. While there are no randomized controlled trials of isoproterenol use for *torsades* in humans (it has prevented quinine-induced *torsades* in a dog model), occasional case reports suggest benefit (Omar et al. 2014). It is probably particularly useful as a bridge to temporary pacing in patients unresponsive to magnesium sulfate.

Transvenous pacing increases heart rate, prevents pauses, and can suppress or abolish episodes of *torsades*. Case reports and case series have suggested benefits from pacing for treating *torsades* induced by quinidine, disopyramide (Keren et al. 1981), sotalol (Totterman et al. 1982), or amitriptyline (Davison 1985), including in patients unresponsive to magnesium sulfate (Charlton et al. 2010).

Early after-depolarizations are facilitated by protein kinases, and there is limited evidence that kinase inhibition may be a viable antiarrhythmic strategy, reducing the inducibility of *torsades* (Mazur et al. 1999). α_2-adrenoceptor agonists attenuate L-type calcium channels and suppress early after-depolarizations. Tsutsui and colleagues (2012) reported promising results were obtained for clonidine and dexmedetomidine, with both drugs shortening the QT interval and reducing the incidence of *torsades* in a rabbit model (Thomas and Behr 2016).

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Chapter 15

A Safety Perspective on Additional Aspects of Drug Development and Therapeutic Use

If our patient is older than, younger than, sicker than, healthier than, ethnically different from, taller, shorter, simply different from the subjects of a study, do the results pertain? The art of clinical decision-making is judgment, an even more difficult concept to grapple with than evidence (Katz 2001).

15.1 Introduction

Previous chapters have focused on cardiovascular safety in drug development and therapeutic use. In this final chapter, we provide a flavor of safety considerations in other aspects of integrated biopharmaceutical medicine, a discipline that encompasses drug development, commercial-scale manufacture, prescription by physicians, dispensing by pharmacists, and the administration of medicines (both by patients themselves and by caretakers, hospital staff, and residential care staff).

Six areas are discussed. While these have been chosen arbitrarily, each one allows additional commentary on the general topic of drug safety. These areas include regulatory science, rare diseases, precision medicine, pain medication, adherence, and the reporting of randomized clinical trials.

15.2 Regulatory Science

In addition to biological, clinical, statistical, and manufacturing sciences, regulatory science is a key component of medical product development. In a talk given on October 6, 2010, in Washington, DC, FDA Commissioner Dr Margaret Hamburg announced the release of a White Paper entitled "Advancing Regulatory Science for Public Health: A Framework for FDA's Regulatory Science Initiative." She noted that regulatory science refers to "the science and tools needed to assess and evaluate a product's safety, efficacy, quality and performance. Regulatory science involves the development of new methods, standards and models we can use to speed the development, review, approval and ongoing oversight of medical products" (Hamburg 2010). In August 2011, the agency

J.R. Turner et al., *Cardiovascular Safety in Drug Development and Therapeutic Use*, DOI 10.1007/978-3-319-40347-2_15

Table 15.1 Priority areas of regulatory science at FDA

1. Modernize toxicology to enhance product safety
2. Stimulate innovation in clinical evaluations and personalized medicine to improve product development and patient outcomes
3. Support new approaches to improve product manufacturing and quality
4. Ensure FDA readiness to evaluate innovative emerging technologies
5. Harness diverse data through information sciences to improve health outcomes
6. Implement a new prevention-focused food safety system to protect public health
7. Facilitate development of medical countermeasures to protect against threats to USA and global health and security
8. Strengthen social and behavioral science to help consumers and professionals make informed decisions about regulated products
9. Strengthen the global product safety net

released its document entitled "Advancing Regulatory Science at FDA: A Strategic Plan" (FDA 2011). The plan identified eight priority areas of regulatory science where new or enhanced engagement in regulatory science research was considered essential to the continued success of FDA's public health and regulatory mission. A ninth strategic priority was added in 2013. These priorities are presented in Table 15.1.

15.2.1 Contributors to the Development of Regulatory Science

In addition to regulatory agencies, other stakeholders play major roles in advancing regulatory science. Academic medical centers have considerable scientific expertise, and interaction between regulators and academicians can help shape "the regulatory science agenda" (Meyer 2014). Experts from industry also play an important role. As a result of the contributions and collaborations of experts from this triumvirate of stakeholders, consortia are playing a particularly significant role in the advancement of regulatory science. Since its launch in Europe in 2008, the Innovative Medicines Initiative "has catalyzed the formation of many consortia to address challenges in drug development and regulation" (Goldman et al. 2015). These authors highlighted key outcomes and lessons learned to date.

Consortia are also important to the FDA's involvement in the advancement of regulatory science (Woodcock et al. 2014). Since their Critical Path Initiative was launched in 2004 (FDA 2004), FDA's Center for Drug Evaluation and Research is now participating in more than 20 science-driven consortia to improve the science of drug development and regulation (Woodcock 2014). One of these, the Cardiac Safety Research Consortium, was introduced in Chap. 1.

15.3 Rare Diseases

Definitions of a rare disease differ by country, being influenced by the size of the population in a given country. In the USA, a rare disease, also referred to as an orphan disease, is defined as one that affects fewer than 200,000 patients. While that number may initially seem small when compared with estimates of individuals in the USA with, for example, hypertension and diabetes (both of which affect tens of millions of individuals), the tremendous importance of this topic lies in the fact that there are thousands of rare diseases, a total of tens of millions of patients suffer from them, the majority are of genetic origin and life-threatening, and far too few have available treatments (Turner 2012a). Of the estimated 7000 rare diseases, only around 300 have medicines approved to treat them, referred to as orphan drugs: this gap represents "a huge unmet medical need" (Sasinowski et al. 2015).

In 2014 the FDA approved 41 novel new drugs, 17 of which were designated as orphan drugs (FDA 2015a). In 2015 the FDA approved 45 novel new drugs, 21 of which were designated as orphan drugs (FDA 2016). For many of them, the FDA used a combination of various approaches to bring the new drug to market as quickly as possible: the designations for these approaches include fast track, breakthrough, priority review, and accelerated approval. Table 15.2 summarizes the nature of these methods for expediting innovative novel new drugs to market.

A pertinent question for both a regulatory agency and a patient (or, in the case of many rare diseases that afflict children, a patient's parents or legal guardian) is: How much risk are we prepared to take to obtain the therapeutic benefit of a drug for this serious and potentially fatal disease? The statement in the FDA's Sentinel Initiative that we first encountered in Chap. 1 is particularly pertinent here (FDA 2008):

> Although marketed medical products are required by federal law to be safe for their intended use, *safety does not mean zero risk*. A safe product is one that has acceptable risks, given the magnitude of benefit expected in a specific population and within the context of alternatives available.

When there is no other therapy available for a serious and potentially fatal disease, it is a perfectly reasonable decision to accept more risk than when approving (and taking) a drug for a much less serious condition, especially one for which there are already available therapies.

15.4 Precision Medicine

While the term personalized medicine is used widely in the literature to refer to the tailoring of an intervention for an individual based on specific (often genetic) information pertaining to that individual, in almost all cases, the term precision medicine

Table 15.2 FDA methods for expediting innovative novel new drugs to market

Method designation	Description
Fast track	Fast track is for drugs with the potential to address unmet medical needs. Fast track speeds new drug development and review. One example is increasing the level of communication FDA allocates to drug developers and by enabling CDER to review portions of a drug application ahead of the submission of the complete application
Breakthrough	Breakthrough therapies are drugs with preliminary clinical evidence demonstrating that the drug may result in substantial improvement in at least one clinically significant endpoint over other available therapies. All of the fast track program features are included in addition to more intensive FDA guidance on an efficient drug development program. Breakthrough status is designed to help shorten the development time of a promising new therapy
Priority review	A priority review designation means that CDER determined that the drug has the potential to provide a significant advance in medical care and set a target to review the drug within 6 months instead of the standard 10 months
Accelerated approval	The accelerated approval program allows early approval of a drug for a serious or life-threatening illness that offers a benefit over current treatments. Approval is based on a surrogate endpoint or other clinical measures that are considered reasonably likely to predict a clinical benefit of the drug. Once accelerated approval is granted, the drug must undergo additional testing to confirm its therapeutic benefit. This strategy speeds the availability of the drug to patients who need it

Source: FDA (2015a)

can reasonably and forcefully be argued to be more appropriate (an example of an exception occurs when a cancer vaccine's manufacture incorporates the use of an individual patient's material in preparing a treatment uniquely tailored to that individual: see Kaitin (2008). Physicians have always practiced personalized medicine to the limit of knowledge at any given point in time. Clinical care of a patient has always involved, and will continue to involve, using all available evidence concerning the patient's unique set of characteristics and circumstances (physical, psychosocial, sociocultural, socioeconomic, environmental) and knowledge of all available treatment options to tailor optimal treatment for the patient.

Throughout history, and particularly when multiple generations lived in the same town and were cared for by the same physician over the course of his or her (all too often his) career, the physician may have incorporated knowledge of health and disease states of older members of a patient's family in the diagnostic process. In this scenario, it can be reasonably argued that genetic information was being employed, even though the molecular biology of transmission genetics was not known at the time. Now, with the completion of the Human Genome Project and the public availability of huge amounts of disease-related data, genomic technology permits highly accurate prediction of individuals who will and who will not likely benefit from a particular drug (see (Turner and Durham 2009)). In the case of some cytotoxic oncology drugs, it also predicts who cannot receive therapeutic benefit from a drug but who can certainly be harmed by it: the benefit–risk balance of treatment with the

drug is therefore immediately unfavorable for that individual (Lee and Turner 2016). For example, crizotinib and vemurafenib were approved by the FDA in 2011 in combination with FDA-approved companion diagnostic tests. Crizotinib is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer that is anaplastic lymphoma kinase (ALK) positive as detected by the associated FDA-approved test. Vemurafenib, indicated for melanoma, is only indicated for patients with a certain abnormal variant of the BRAF gene, $BRAF^{V600E}$, as identified by the associated FDA-approved test (Turner 2012b).

In the context of employing pharmacogenomic biomarkers in the prediction of severe adverse drug reactions, Ingelman–Sundberg commented in an editorial piece in the *New England Journal of Medicine* as follows (2008, p. 637):

> The search for pharmacogenomic markers that could be used to identify patients at increased risk for drug-related toxic effects has often focused on variation within genes encoding drug-metabolizing enzymes. Altered enzymatic activity can lead to elevated levels of the substrate drug, or, alternatively, increased amounts of a reactive metabolite, either of which could have toxic effects.

The editorial focused on the antiretroviral drug abacavir, used against infection with the human immunodeficiency virus and discussed in an article by Mallal and colleagues describing original research published in the same issue of the journal (Mallal et al. 2008). In white populations, about 6 % of individuals carry the HLA-B*5701 allele, a genetic variant strongly associated with hypersensitivity to abacavir (it is unknown why the association between HLA-B alleles and hypersensitivity is less clear in black populations). When a physician is considering prescribing abacavir for a patient, screening that individual for the presence of the HLA-B*5701 allele has proved successful in reducing hypersensitivity reactions to the drug.

15.5 Pain Medication: Abuse of Prescription Opioids

Pain is a ubiquitous consequence of a wide range of injuries, surgeries, and medical conditions as diverse as cancer, low-back pain, and restless leg syndrome (Ahmedzai et al. 2012; Cloutier et al. 2013; Trenkwalder et al. 2013). Both acute and chronic pain can be extremely debilitating clinical conditions, and there is a constant need for analgesics in medical practice.

Assessing pain is not as straightforward as might initially be thought: as Joffe and colleagues noted, “To effectively treat pain, it must be detected and quantified using a validated assessment tool” (Joffe et al. 2013). Pain assessment becomes even more challenging when an individual who is almost certainly experiencing severe pain is unable to self-report the pain: examples include patients in cardiovascular intensive care units and medical/surgical/trauma units (Rose et al. 2013).

Opium poppy produces benzylisoquinoline alkaloids (opiates) that are important medicinal compounds, including the analgesics morphine, codeine, and thebaine, which are used in the synthesis of various semisynthetic opioid analgesics

(Pasternak and Pan 2013; Runguphan et al. 2012). These synthesized compounds include hydrocodone, oxycodone, hydromorphone, and oxymorphone. Millions of patients are treated with opioid analgesics (Alexander et al. 2014). Patients requiring chronic opioid administration often have complex medical conditions, and they do not all respond in the same manner, leading to unpredictable individual differences in effectiveness and adverse drug reactions.

Drug addiction can be described as "a chronically relapsing disorder characterized by the compulsive desire to use drugs and a loss of control over consumption" (Prud'homme et al. 2015). There are increasing concerns regarding the health consequences of long-term opioid abuse (Herzig 2015). Dennis and colleagues observed that "The consequences of opioid relapse among patients being treated with opioid substitution treatment are serious and can result in abnormal cardiovascular function, overdose, and mortality" (Dennis et al. 2015). Interventions for the management of addictive behaviors and opioid dependence are therefore important (Prud'homme et al. 2015; Soyka 2015; Reed et al. 2015).

A pharmaceutical research area of considerable current interest is the development of abuse-deterrent opioids. The FDA's April 2015 Guidance for Industry entitled "Abuse-deterrent opioids: Evaluation and Labeling" commented as follows (FDA 2015b):

> Prescription opioid products are an important component of modern pain management. However, abuse and misuse of these products have created a serious and growing public health problem. One potentially important step towards the goal of creating safer opioid analgesics has been the development of opioids that are formulated to deter abuse. FDA considers the development of these products a high public health priority.
>
> Because opioid products are often manipulated for purposes of abuse by different routes of administration or to defeat extended-release (ER) properties, most abuse-deterrent technologies developed to date are intended to make manipulation more difficult or to make abuse of the manipulated product less attractive or less rewarding. It should be noted that these technologies have not yet proven successful at deterring the most common form of abuse—swallowing a number of intact capsules or tablets to achieve a feeling of euphoria. Moreover, the fact that a product has abuse-deterrent properties does not mean that there is no risk of abuse. It means, rather, that the risk of abuse is lower than it would be without such properties.

While not necessarily eliminating abuse, reducing it is a very meaningful step forward, and the development of abuse-deterrent formulations is therefore an important area of research (Alexander et al. 2014; Mastropietro and Omidian 2015).

While the final manuscript of this manuscript was being prepared, Dr Robert Califf was sworn in as the new FDA Commissioner in February 2016. Shortly before, he and colleagues from the FDA published a Special Report entitled "A Proactive Response to Prescription Opioid Abuse" in the *New England Journal of Medicine* (Califf et al. 2016). The final paragraph commented as follows:

> Nationally, the annual number of deaths from opioid overdoses now exceeds the number of deaths caused by motor vehicle accidents [reference CDC website]. Regardless of whether we view these issues from the perspective of patients, physicians, or regulators, the status quo is clearly not acceptable. As the public health agency responsible for oversight of pharmaceutical safety and effectiveness, we recognize that this crisis demands solutions. We are committed to action, and we urge others to join us.

15.6 Adherence

The goal of FDA's *Safe Use Initiative* is: "to reduce preventable harm by identifying specific, preventable medication risks and developing, implementing and evaluating cross-sector interventions with partners who are committed to safe medication use" (FDA 2015c). Medication adherence is one of the areas in which collaboration by multiple stakeholders is welcomed.

As noted in Chap. 3, hypertension is commonly designated as the greatest contributor to the global burden of disease. As Dolan and O'Brien (2013) noted, "Ischaemic heart disease, ischaemic, non-ischaemic and haemorrhagic stroke, hypertensive heart disease, atrial fibrillation and flutter, peripheral vascular disease, aortic aneurysm and chronic renal disease (to which we must now add cognitive impairment and dementia) are all attributed to hypertension." Of particular relevance to discussions here is the fact that, as Dolan and O'Brien highlighted, there are many pharmacological agents on the market that, if used appropriately, provide therapeutic benefit. Additional new drugs, particularly single-pill combinations with enhanced benefit-safety-value profiles, will always be welcome, but their development is not the limiting factor here: Nieuwlaat and colleagues (2013) observed that learning how to implement effective therapies for cardiovascular disease in a better manner will have a larger effect on patient outcomes than most single new drugs.

With regard to patients, and as noted in the previous chapter, Howren (2013) observed that "Adherence is a term used to describe the extent to which an individual's behavior coincides with health-related instructions or recommendations given by a health care provider in the context of a specific disease or disorder." While the negative effect of patient nonadherence has been known for decades, some authoritative sources still put average nonadherence among those with chronic diseases around 50 % (Brown and Bussell 2011), and the American Heart Association (AHA) observes that "It is estimated that three out of four Americans do not take their medication as directed" (AHA 2016).

Improving hypertension management requires improvements at both the patient and physician levels. At the patient level, considerations include patient education and empowerment. Considerations at the physician level include improving their knowledge of the cognitive and behavioral factors involved in patients' active engagement in their own care and the manner in which they communicate with patients (Turner 2013). The interaction between patient and physician is important in improving patient adherence. In the context of statin therapy, for example, Schedlbauer and colleagues observed that increased patient centeredness, i.e., placing emphasis on patients' perspective and engaging in shared decision-making, might be useful (Schedlbauer et al. 2010). The importance of communication between doctor and patient has been known for decades (see (Korsch et al. 1968; Roter and Hall 2013)), but it is still not optimal. Levinson and colleagues, for example, observed that patient-centered communication skills that enhance patient satisfaction, treatment adherence, and self-management "can be effectively taught at all levels of medical education and to practicing physicians," yet most physicians receive limited training in these skills (Levinson et al. 2010).

Before discussing a different aspect of adherence, physician nonadherence to prescribing guidelines, it should be acknowledged that there are many hypertension specialists who are extremely conversant with prescribing guidelines, who communicate very well with their patients, and who sometimes recommend treatment for specific patients that differs from the guidelines because they genuinely believe that such action is warranted. This is certainly within the spirit of guidelines, which acknowledge the role of a physician's expertise and clinical experience. However, the literature reveals that deviation from guideline-recommended treatment is not always a considered, deliberate action.

Awareness of prescriber nonadherence to hypertension treatment guidelines dates back at least to the 1990s (see (Cabana et al. 1999)). As one example of the financial ramifications, consider a retrospective analysis of year-2006 Medical Expenditure Panel Survey data reporting substantial costs of inappropriate hypertension management. Using year-2006 US dollars, the author noted that the "overall prevalence of hypertension was estimated at 19.7 %, with 36 % of identified patients treated inappropriately. The per-person cost for inappropriate treatment was $234.60, and the total national cost was approximately $13 billion" (Balu 2009). While human costs are harder to quantify, they are no doubt commensurately disturbing (Turner 2013).

With regard to offering suggestions regarding how adherence may be improved, we [JRT] have previously proposed several pragmatic approaches with the hopes of raising both eyebrows and interest (Richards and Turner 2012; Turner and Strumph 2012). One is that every biopharmaceutical company with one or more marketed products should appoint a chief adherence officer, affording this person the same gravitas given to all other occupants of the company's "C-wing" (e.g., the chief executive officer and the chief medical officer). This individual should ideally be trained, or at least be willing to become rapidly immersed, in educational and behavioral sciences as well as biological and pharmaceutical sciences. A second suggestion is that schools of medicine, pharmacy, nursing, and allied health professions need to redouble attention to the adherence component of their curricula in novel ways. We readily acknowledge that there are always time pressures in professional training programs, but why not try the following: Devote a 1-h lecture slot shortly before students interact with patients for the first time to having them write, by hand, the following statement over and over: "I must discuss medication adherence with my patients at every possible opportunity." We feel that students would not readily forget that experience. More rigorously supported suggestions for improving adherence to antihypertensive medications have been offered by Turner (2013).

As a second example, consider allergic rhinitis, one of the most common diseases affecting adults. In the pediatric population, it is the most common chronic disease in the USA, which contributes to making it the fifth most common chronic disease in the USA overall. Allergic rhinitis can impair quality of life and, through loss of work and school attendance, is responsible for as much as $2–$4 billion in lost productivity annually (Seidman et al. 2015). Bender (2015) summarized several studies on adherence to allergic rhinitis treatments, the investigation of which has some challenges. These arise from the fact that many treatments are taken as

needed: the lack of an administration schedule therefore complicates assessment of adherence. Additionally, many patients take over-the-counter medication without consulting a physician. However, as intranasal corticosteroids are a prescribed daily treatment, more research has been conducted in this area: adherence rates are around 50 % or lower.

Evidence for adherence to immunotherapy interventions is no more encouraging. Three to five years of sustained immunotherapy is required for full, long-term benefits (Marogna et al. 2010), and "the cost and effort of immunotherapy are difficult to justify in the face of poor adherence" (Bender 2015). With regard to estimates of the consequences of nonadherence across multiple chronic diseases, including hypertension, hyperlipidemia, chronic obstructive pulmonary disease, and diabetes, costs of $300 billion in excess health-care costs and 125,000 deaths per year are reasonable figures (see (Bender 2015)).

Unfortunately, a review of multiple publications describing various types of intervention currently paints a collectively discouraging picture: nonadherence is truly an obdurate opponent of good health. Also unfortunately, nonadherence has multiple causes, combinations of which differ between individuals. When trying to predict nonadherence, some predictors are difficult or simply not possible to modify: these include race, age, socioeconomic status, medication costs, and treatment duration. Therefore, it is sensible to focus on modifiable factors that can be influenced by health-care providers. Bender (2015) provided practical recommendations for strategies that can improve adherence: while some are couched in terms of allergy practice, many can be generalized to other conditions. These include providing patient-centered care, adopting the chronic care model (which integrates patient-, provider-, and system-level interventions), building trusting relationships with patients, improving providers' listening skills, providing educational opportunities for patients to learn more about their disease(s), and engaging in more comprehensive follow-up strategies. The latter can be facilitated with very minimal time demand by utilizing technologies such as text messaging and interactive voice recognition technology.

15.7 Reporting Randomized Clinical Trials

Previous chapters have described preapproval clinical trials specifically designed to investigate cardiovascular safety during drug development, with the goal of prospectively excluding unacceptable cardiovascular risk: they have also addressed examples of trials conducted in the postmarketing arena. Discussions in this section turn to the topic of how randomized clinical trials should be reported.

While it is extremely important that all clinical trials are designed appropriately, conducted meticulously, and analyzed appropriately and correctly, it is equally important that they are reported appropriately. Published reports, typically papers in peer-reviewed journals, are used by physicians practicing evidence-based medicine to decide if the treatment discussed in a paper is an appropriate one for a given

patient. Physicians must therefore be given accurate and complete results addressing both efficacy and safety data that are presented in a transparent manner. Publications reporting individual studies can also be used by groups of experts representing professional societies to write treatment guidelines based on their review of all relevant study reports, again bearing witness to the need for optimal-quality reporting of the original studies.

In the early 1990s, there was concern among many researchers and journal editors that reporting of clinical trials was not as good as it should be. This concern led to various meetings that generated the Consolidated Standards of Reporting Trials (CONSORT) Statement (see CONSORT Group 2016). CONSORT is "a set of reporting recommendations – it does not make statements on how trials should be done, but asks that what was done should be fully and accurately reported" (Altman et al. 2001). First published in 1996 (Begg et al. 1996) and revised in 2001 (Moher et al. 2001), the statement includes a checklist of items that should be included in the report of a clinical trial. These items are regularly reviewed, and the CONSORT 2010 checklist is available on the group's web site (see also (Moher et al. 2010)). The checklist addresses the following sections of a publication: Title and Abstract, Introduction, Methods, Results, Discussion, and Other Information (e.g., the trial's registration number and sources of funding and other support). Within these sections, there are a total of 25 checklist items. Many (but certainly not all) journals now require that manuscripts submitted to them conform to the guidelines presented in the statement.

The original CONSORT statement addressed one research design that was particularly common at the time the statement was published, i.e., the randomized, concurrently controlled clinical trial employing two treatment groups. Given that other trial designs have now also become common, extension statements have been released addressing various designs including cluster trials, noninferiority and equivalence trials, and pragmatic trials. Other examples of extension statements include those addressing non-pharmacologic interventions, patient reported outcomes, and harms.

15.7.1 The CONSORT Extension Statement Addressing Drug Harms

The original CONSORT statement primarily aimed at improving the quality of reporting efficacy data. The 2001 revision saw the addition of one item regarding the reporting of adverse events, but it was later felt not to do "full justice to the importance of harms-related issues," leading a 2004 extension statement to address this topic in considerable detail (Ioannidis et al. 2004). Before summarizing the extension statement's recommendations, the nomenclature employed warrants our attention. The terms safety and harm were discussed in Sect. 1.2, and our rationale for using the term safety in this book was couched in terms of the overreaction of print, radio, and television media to any mention of the term "drug harm." Ioannidis

Table 15.3 Recommendations of the CONSORT extension statement on harms

The title or abstract should state if the study collected data on harms and benefits
The introduction should state if the trial assessed harms and benefits
List monitored adverse events with definitions for each and, when relevant, classify expected events vs. unexpected events, reference to standardized and validated definitions, as well as the description of new definitions
Clarify how the information related to harms was collected
Describe plans for presenting and analyzing information on harms, including coding, management of recurring events, specification of time of monitoring of adverse events, management of continuous measures, as well as any statistical analysis
Describe for each study arm the participant withdrawals due to harms and the experience with the allocated treatment
Provide the denominators for analyses on harms
Present the absolute risk per study arm and type of adverse effect
Describe some analysis and exploratory analysis for subgroup harms

and colleagues presented an alternative argument, commenting as follows, using "RCTs" as an abbreviation for randomized clinical trials (Ioannidis et al. 2004):

> The terminology of harms-related issues in RCTs is confusing and often misleading or misused. "Safety" is a reassuring term that may obscure the real and potentially major "harms" that drugs and other interventions may cause. We encourage authors to use the term "harms" instead of "safety." In addition to misused terminology, reporting of harms in RCTs has received less attention than reporting of efficacy and effectiveness and is often inadequate. In short, both scientific evidence and ethical necessity call for action to improve the quality of reporting of harms in RCTs.

We certainly respect these authors' perspective: indeed, we noted in our discussions in Sect. 1.2 that it is actually harm that is measured, with lesser harm then being equated to greater safety in a gradated manner. Nonetheless, it is likely fair to say that the term safety continues to be predominantly used in the literature.

Table 15.3 presents the recommendations of the CONSORT extension statement on harms.

15.7.2 Imperfections in Reporting Randomized Clinical Trials

Unfortunately, despite the best intentions of CONSORT, perfection is not the norm. Moher and colleagues observed that "Overwhelming evidence shows the quality of reporting of randomized controlled trials (RCTs) is not optimal" (Moher et al. 2010). More recent papers presented in the respective section of this chapter's Further Reading list provide similar commentary. The lack of completeness in reporting compounds physicians' difficulty in determining the generalizability of information provided in study reports to their patients. As one example in the cardiovascular domain, Magin and colleagues investigated how completely socioeconomic data were presented in studies reporting trials of stroke or transient ischemic

attack published in 12 major journals subsequent to the release of the revised CONSORT statement: the journals published papers in the disciplines of general medicine, general neurology, cerebrovascular disease, and rehabilitation. Socioeconomic status is associated with access to care and with post-stroke outcomes including mortality, functional outcome, recurrent stroke, and hospital readmission. Disturbingly, only 12 % of the studies included in their review reported any measure of socioeconomic status. As the authors concluded, "Improving reporting of [socioeconomic status] could enhance clinicians' ability to evaluate RCT findings and apply them to their patients" (Magin et al. 2013).

Maggi and colleagues took a different approach to evaluating the degree to which published reports of randomized clinical trials adhered to CONSORT recommendations with regard to adverse event reporting (Maggi et al. 2014). They chose to focus on four leading medical journals with very high impact factors: *New England Journal of Medicine, Lancet, Journal of the American Medical Association,* and the *British Medical Journal.* Using the Medline search engine, 122 randomized clinical trials published in 2009, 5 years after the publication of the CONSORT extension statement on harms, were identified. The most frequently met CONSORT recommendation was mention of harms in the papers' title or abstract (72.1 % of the papers analyzed). The recommendation most infrequently met was the reporting of how harm information was collected (10.7 %).

A similarly bleak picture was presented by Sivendran and colleagues, who evaluated adverse event reporting in 175 reports of oncology randomized clinical trials, identified using the Medline, PubMed, and Embase search engines, published in the 3 years 2009–2011 (Sivendran et al. 2014). Of the studies, 88 % grouped together adverse events of varying severity, and 37 % did not specify the criteria used to select which events were reported. The authors concluded as follows: "Reporting of adverse events in oncology publications of randomized trials is suboptimal and characterized by substantial selectivity and heterogeneity. The development of oncology-specific standards for adverse event reporting should be established to ensure consistency and provide critical information required for medical decision-making" (Sivendran et al. 2014).

There is clearly much room for improvement by authors, manuscript reviewers, and journal editors in ensuring that readers of randomized clinical trial reports are provided with comprehensive descriptions of adverse event data.

15.7.3 Public Registration of Clinical Trials

In a 2004 perspective article published in the *New England Journal of Medicine*, Steinbrook (2004) commented as follows:

> For many years, the registration in a public data bank of all clinical trials — from start to completion and reporting of results — has seemed a quixotic quest of some academic researchers, medical-journal editors, and librarians. Within the past two months, however, a constellation of events and developments has broadened this effort and captured the

> attention of the medical profession, the news media, and government officials…Although uncertainties are ahead, there is a growing realization that the public registration of clinical trials is an idea whose time has come. In the long term, no one benefits from the selective release of information about trials and the selective reporting of results.

Registration and reporting of trials in this manner are now routine practice. ClinicalTrials.gov is "a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world" (www.ClinicalTrials.gov). On the day this sentence was written on January 1, 2016, it listed 205,641 studies, with locations in all 50 states in the USA and in 191 countries.

Given that trials' results are typically presented on ClinicalTrials.gov and in journal publications, it would seem eminently reasonable to expect the presented results to be identical in both places. However, this is not always the case. Riveros and colleagues observed that "Trial results, especially serious adverse events, are more completely reported at ClinicalTrials.gov than in the published article" (Riveros et al. 2013). Hartung and colleagues observed as follows: "Reporting discrepancies between the ClinicalTrials.gov results database and matching publications are common. Which source contains the more accurate account of results is unclear, although ClinicalTrials.gov may provide a more comprehensive description of adverse events than the publication" (Hartung et al. 2014). Earley and colleagues commented as follows: "Deaths are variably reported in ClinicalTrials.gov records. A reliable total number of deaths per arm cannot always be determined with certainty or can be discordant with the number reported in corresponding trial publications. This highlights a need for unambiguous and complete reporting of the number of deaths in trial registries and publications" (Earley et al. 2013). Tang and colleagues compared the consistency between serious adverse events posted at ClinicalTrials.gov and those published in corresponding journals (Tang et al. 2015). They concluded that many trials with serious adverse events posted at ClinicalTrials.gov omit the reporting of these events in corresponding publications, or report a discrepant number as compared with ClinicalTrials.gov, commenting that "These results underline the need to consult ClinicalTrials.gov for more information on serious harms."

While public registration and reporting of clinical trials are an excellent idea, here too it appears that we have much room for improvement.

15.7.4 Evidence-Based Medicine and the Challenge of Generalizability

Imagine that a randomized clinical study has been perfectly reported. Imagine also that a physician wishes to use the information presented to help decide if the treatment discussed will be useful for a specific patient under his or her care, where "useful" can be operationally defined as having a favorable benefit–risk balance. That is, can the information presented in the paper, which was generated from the

set of participants employed in the trial, be generalized to this patient? Physician–scientist David Katz, whose work we first met in the previous chapter, addressed the issue of generalizability as follows (Katz 2001, p. xi):

> The inapplicability of some evidence to some patients is self-evident. Studies of prostate cancer are irrelevant to our female patients; studies of cervical cancer are irrelevant to our male patients. Yet beyond the obvious exclusions is a vast sea of gray. If our patient is older than, younger than, sicker than, healthier than, ethnically different from, taller, shorter, simply different from the subjects of a study, do the results pertain?

While the art of clinical decision-making is of paramount importance, it is beyond the scope of this book. That said, discussions in this section are certainly relevant. This section started with the words "Imagine that a randomized clinical study has been perfectly reported," and we then considered a physician's use of the information presented in the publication. In conjunction with his or her patients, a decision is made as to whether or not the drug has a favorable benefit–risk balance on a patient-by-patient basis. The sentiments expressed succinctly but powerfully by Katz make it clear that, even given perfectly reported information from a trial, physicians have to use clinical judgment to arrive at their best estimation of the benefit–risk balance for each individual patient. Now consider how much more imprecise a physician's determination of benefit–risk balance will likely be if the information in the publication is less than comprehensive with regard to both efficacy and safety. Little consideration is needed to reach the conclusion that, as for a trial's study design, conduct, and analysis, its reporting must be of optimal quality.

15.8 Concluding Comments

As was noted in the first chapter of this book, it is an unfortunate but immutable fact that no biologically active drug is free from the possibility of causing adverse reactions in certain individuals who are genetically and/or environmentally susceptible. However, it is also a patient-centric and public health moral imperative to do everything we can to eliminate preventable adverse drug reactions, including adverse cardiovascular reactions. We hope that you have found this book to be helpful in expanding your knowledge and understanding of cardiovascular safety and that some of you may wish to become involved (or more involved) in this central component of drug safety in development and therapeutic use.

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Further Readings by Topic

In this chapter the Further Reading list is broken into seven sections. The first six address the topics discussed in the text of the chapter, and the seventh provides publications addressing a multitude of other topics in the expansive realm of integrated pharmaceutical medicine.

Regulatory Science

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Afterword

The preceding chapters present a snapshot in time of the book's topic, cardiovascular safety in drug development and therapeutic use. While foundational material in Part II and Part III will not change dramatically in the foreseeable future, the Early QTc Assessment Initiative and the CiPA Initiative (discussed in Chaps. 8 and 9, respectively) are progressing quite rapidly. We updated those discussions to the greatest extent possible just before submitting the final manuscript to our publisher at the beginning of April 2016. Having just completed reviewing the galley proofs, this Afterword allows us to provide some additional updates and references. We also provide additional thoughts on the use of cardiovascular outcome studies in the prospective exclusion of unacceptable cardiovascular risk associated with new antidiabetic drugs for type 2 diabetes, the topic of discussions in Chaps. 12 and 13.

In a paper published electronically on June 24, 2016, Murphy and colleagues (Murphy et al. 2016) reported the use of concentration response (CR) modeling applied to data from two multiple ascending dose studies to examine the potential of lemborexant, a novel dual orexin receptor antagonist being developed to treat insomnia, to cause QT prolongation. The authors concluded as follows:

> CR modeling of data from early phase clinical studies, including plasma levels far exceeding those anticipated clinically, indicated that a QT effect >10 msec could be excluded. Regulatory agreement with this methodology demonstrates the effectiveness of a CR modeling approach as an alternative to thorough QT studies.

In a paper published electronically on June 8, 2016, Colatsky and colleagues (2016) provided an update on the progress of the CiPA initiative. Their paper concluded as follows:

> Since the initial public discussion of CiPA in July 2013, there has been a concerted international effort to define, standardize, and validate the human ion channel assays, define the metrics of the in silico model, test and validate [human cardiac stem cell-derived cardiomyocyte-based] approaches, and define and test Phase 1 ECG biomarkers. Significant scientific progress has been made and the CiPA effort is on track to complete the necessary work by the end of 2017. The CiPA Steering Committee is providing the ICH S7B/E14

J.R. Turner et al., *Cardiovascular Safety in Drug Development and Therapeutic Use*, DOI 10.1007/978-3-319-40347-2

Discussion Group with on-going updates on working group progress and seeking input from ICH on the regulatory implementation of CiPA as the effort evolves over the next ~1.5 years.

There is less specific progress to report on the third topic addressed in this Afterword, the investigation of potential cardiovascular risk associated with new antidiabetic drugs for type 2 diabetes. That said, the one of the currently ongoing CSRC projects is entitled "The Restricted Mean Survival Time (RMST) statistical analysis approach for analyzing diabetes cardiovascular outcomes trials." The employment of RMST analysis in this domain was introduced in Sect. 13.5.3, and future developments will be of considerable interest to many clinicians and scientists.

In a departure from the central educational mission of this book, we wish to share here a personal but nonetheless reasoned opinion held by the authors. We strongly believe that the Rosiglitazone Case Study described in Chap. 12 will not be viewed kindly by historians of pharmaceutical medicine. Section 12.2.1 discussed the seminal meta-analysis published by Nissen and Wolski just over 9 years ago (Nissen and Wolski 2007), and listed limitations stated by the authors themselves as well as limitations discussed by other researchers. It should be noted that a similar meta-analysis was performed by the FDA in 2007, using participant-level data available with the regulatory agency (see Panicker et al. 2012). For myocardial infarction in the rosiglitazone group compared with the control group, the odds (relative risk) ratio was 1.5 (95% CI: 0.9–2.7), a difference between treatment groups that was not statistically significant. The differing conclusions from different meta-analyses of these studies, which it must be remembered were not designed to assess cardiovascular safety, sparked considerable controversy (Panicker et al. 2012): since the risk of adverse cardiovascular outcomes was rare, inclusion or exclusion of a few trials in the meta-analyses performed by different groups completely changed their conclusions.

The response of regulatory agencies was twofold: first, to reconsider marketing approvals for rosiglitazone; and second, to put in place guidelines for evaluating the cardiovascular safety of future candidate drugs. The latter, though welcome to many and done with noble intent, was probably not justified solely on the basis of the rosiglitazone experience, as is borne out by the FDA's December 2015 statement discussed in Sect. 12.5. Given that statement, it can reasonably be argued that there are currently burdensome regulatory landscapes in the USA and Europe for all new antidiabetic drugs for type 2 diabetes that were driven by a purported increase in cardiovascular (myocardial infarction) risk for one antidiabetic drug that has subsequently been refuted by an influential regulatory agency. Nissen and Wolski's (2007) written statement that "A meta-analysis is always considered less convincing than a large prospective trial designed to assess the outcome of interest" stands in stark contrast to their concurrent and vociferous exhortations for the result of their analysis to change the practice of antidiabetic pharmaceutical medicine overnight by removing rosiglitazone from the market.

To its credit, the FDA's December 2015 statement, delivered with appropriate clinical decorum and based on enormous cardiovascular safety monitoring rather than the single risk ratio point estimate and its associated confidence interval that started this case study in 2007, effectively exonerates rosiglitazone from an unacceptable cardiovascular risk. While pleasing to many clinical scientists, however, it

is a pyrrhic victory. What is now seen by the FDA as a therapeutically useful drug with a favorable benefit-risk balance has been removed from the market in multiple countries, and, while it remains available to patients in the USA, one suspects that it will be prescribed for very few. Uncounted millions of patients for whom there remains a great medical need have therefore been deprived of a treatment option.

We leave you with three final thoughts. First, the rosiglitazone case study led the cardiovascular safety community to adopt specified margins of safety, and also to develop rules on the conduct and analysis of cardiovascular safety studies and data that can make this assessment more valid and reliable when it is felt that such assessment is truly warranted. Second, the EMPA-REG cardiovascular outcome study discussed in Chap. 13 revealed that empagliflozin was associated with a statistically significant ($P=0.04$) 14 % decrease in cardiovascular risk (Zinman et al. 2015). As the authors observed, "Patients with type 2 diabetes at high risk for cardiovascular events who received empagliflozin, as compared with placebo, had a lower rate of the primary composite cardiovascular outcome and of death from any cause when the study drug was added to standard care." Discussions of the clinical implications of this study's results can be found in the literature (Perseghin and Solini 2016). Third, the case study illustrates the difficulties in achieving the delicate balance between ensuring that effective medicines are available to patients with minimum delay while also needing to ensure their safety, especially when the risk of adverse outcomes may be manifest only after several years. It also demonstrates how pressure from the media makes the regulators' task even more difficult. As noted at the end of Chap. 13, this area of cardiovascular safety necessitates continued dialogue in the scientific, clinical, and regulatory communities.

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July 4, 2016

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